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ADVANCES *in* INTERNAL MEDICINE

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Pathogenesis and Treatment of Renal Lithiasis—Newer Concepts*

ARTHUR J BUTT

Butt Medical Foundation Baptist Hospital Pensacola Fla

MARCET (34) lecturing at Guys Hospital London in 1817 noted when he introduced the subject of urinary calculi "how perfectly novel the chemical history of these bodies was to the great mass of students and how anxious they appeared to avail themselves of the information" He was struck with "the remarkable simplicity which modern chemistry has introduced in the history of calculi compared to the singular scantiness of information which prevailed in this respect 20 or 30 years ago" Even today these comments do not seem inappropriate

None of the many mechanisms proposed to explain the pathogenesis of stone formation do so completely The exact nature of the process of calculogenesis still eludes us as does the relative importance of the various responsible factors Lithiasis as such is not a disease entity and stones can be formed as the result of many different pathologic processes and physicochemical disturbances Each form of concrement building may be caused by different pathologic conditions which in turn may be localized in many different organs

The emphasis formerly placed on the pleomorphism of calculi prevented recognition of the fundamental importance of several physical and biochemical phenomena responsible for the formation and growth of stones During the past quarter century our knowledge of the modi

* Part of the investigation reported here was aided by Navy Contract Number Nonr 926(00) Office of Naval Research

fication of crystal formation under colloidal influence and of the role of "protective colloids in maintaining the constituents of the urine in solution has been considerably advanced

Boyle (10) in 1666 was probably the first to observe that the normal shape of many crystals could be changed by the "addition of other bodies More than a hundred years later Rome de Lisle (45) demonstrated that crystals of sodium chloride formed in the presence of fresh urine were octahedral in shape After another twenty years or more Fourcroy and Vauquelin (22a) and Beudant (8a) produced octahedral crystals of sodium chloride in solutions containing urea

The importance of the process of coagulation in stone formation and other calcifications was first recognized by Meckel von Helmsbach (35) He stated that two factors are essential for the production of calculi *(1)* an organic compound of mucous character in which soluble or poorly soluble material can be deposited and *(2)* a fluid super saturated with petrifying or encrustating substances Ramey (39a) suggested that stone formation might be related to the abnormal crystal forms which occur when the crystalline material is deposited in gelatinous mediums Ord (36 37) was the first to use the term "colloid" in connection with crystallization although not in its modern sense Not until 1909 did Lichtwitz and Rosenbach (32) as well as Schade (48) establish that the unusual solubility of stone forming salts in urine depends upon the presence of "protective colloids" which prevent precipitation, agglomeration, and conglomeration of salts and other colloids

Keyser (30) also showed that the protective colloids profoundly influence the solubility of urinary crystalloids He suggested that a disturbance of this colloid protective mechanism might produce irreversible gel formation and crystalloid precipitation with a resultant formation of concrements He also demonstrated the growth of calculi in animals by increasing the amounts of salts excreted thereby overwhelming the protective colloids Thus the concept of hyperexcretory calculosis was elucidated

In Joly s (29) opinion vitamin A deficiency primarily affects the renal epithelium and thereby the excretion of the urinary colloids The ensuing physicochemical changes result in stone formation Higgins (28) first noted the alkalinuria which was constantly present in rats maintained on a vitamin A deficient diet He then suggested that colloids colloidal suspensions and crystalloids might all be concerned in the formation of urinary calculi Snapper Bendien and Polak (54)

reported that the urinary salts remain in solution by the combined action of certain hydrotropic substances and the stable urinary colloids, particularly chondroitin sulfuric acid and nucleic acid A preponderance of labile colloids e g fibrinogen and mucin upsets this balance

MECHANISM OF RENAL CALCULUS FORMATION

Each minute 125 cc of filtrate passes through the glomeruli and all but 1 cc is reabsorbed in the tubules Although selected substances are restored to the blood by reabsorption in the renal tubules daily from 2 to 4 Gm of relatively insoluble precipitable stone forming salts is excreted in the urine In view of the constant, tremendous concentration of these crystalloids one might be surprised that the renal tubules do not become completely occluded by crystalloid salts What prevents these salts from precipitating and clogging the urinary tract? Why do stones form only in certain individuals? Obviously nature must have provided a defense mechanism against the formation of such deposits In this respect surface phenomena, solubility and supersaturation and colloid behavior are of paramount importance Among these three mechanisms the presence of protective colloids of the correct molecular weight and in sufficient quantity is the most important factor for the prevention of the precipitation of crystalloids from the supersaturated solutions which the urine represents Too low a concentration of the natural protective colloids or too low or too high a molecular weight "sensitizes" the crystalline nuclei stone formation may then start immediately or at least be considerably accelerated

Protective colloids are most effective for the prevention of agglomeration of crystalloids once started agglomeration will be neither reversed nor halted by such colloids Addition of a protective colloid to urine in which a precipitate has already formed does not necessarily increase its solubilization It therefore seems most likely that the protective action of the colloids occurs during the concentration of the glomerular filtrate in the convoluted tubules

Stone formation begins when aggregates of inorganic salts combine to form particles of colloidal dimension Such a solid particle, possessing on its surface a double layer of opposite electric charges is known as a colloidal micelle The comparatively large particles of the internal phase are aggregates of countless numbers of molecules or atoms but

only the surface atoms or molecules of such aggregates carry the electric charges

The protective urinary colloids (lyophilic biocolloids) are large and complex They are highly stable and impart their stability to electro cratic sols The latter consist of particles which easily coagulate under the influence of electrolytes The particles of an electrocratic sol, pro tected by a lyophilic biocolloid will migrate in an electric field only to the extent that the protective colloid will move by itself (26)

In calculous disease *the urine may be considered to be a super* saturated salt solution lacking sufficient protective colloids Precipita tion in such a solution leads to the formation of nuclei composed of small crystals of stone forming salts bound together by and incor porated into a colloidal matrix (Plate 1) The precipitation of a spe *cific salt in the urine is governed by (1)* the ionic concentration of this salt (2) the concentration of other, mutually precipitable, salts *(3)* the urinary pH, and *(4)* the quality and quantity of colloids in the urine If these crystalline nuclei are not readily evacuated the surfaces of the nuclei adsorb coagulable i e nonprotective or lyophobic colloids The latter then become incrusted with the salts present in the supersaturated solution

The actual stone thus consists of a nucleus which is almost invaria bly crystalline *surrounded by amorphous or crystalline colloidal* pre cipitates held together by the so called van der Waals forces In con trast protective colloids coating such salt nuclei would prevent in crustation by neutralizing the van der Waals forces (26)

EFFECT OF TESTICULAR HYALURONIDASE ON URINE

It has been assumed for some time that normal urine contains a mucopolysaccharide possibly chondroitin sulfuric acid hyaluronic acid or a heparin like substance Now it has been definitely estab lished that both chondroitin sulfuric acid and hyaluronic acid are present in urine (3)

In 1950 investigation revealed that subcutaneous administration of testicular hyaluronidase to patients with renal lithiasis caused marked changes in the urine which persisted for several hours to 3 days (11) In a significant number of patients the urine became pale clear and free from both normal and pathologic sediment under dark field il *lumination there was evidence of a pronounced effect on the urinary* colloids Addition of hyaluronidase to voided urine in vitro did not

produce these effects Hauser (27) demonstrated that potassium hyaluronate is a powerful dispersing and peptizing agent which accounts for its protective colloid action. Seifter (15-17 19) then proposed that subcutaneous injection of hyaluronidase releases tissue hyaluronic acid at the site of injection and that this acid or one or more of its breakdown products is excreted in the urine where it acts as an efficient protective colloid

Wohlzogen (55) in a controlled experiment on 2 subjects fed an oxaluria producing diet, confirmed that subcutaneous injection of hyaluronidase prevents urinary turbidity and sedimentation Subsequently Wohlzogen and Brandstetter (56) clarified the turbid urine and reduced the crystalluria of 1 of the 2 oxaluric subjects by orally administered hyaluronic acid Sanjurgo (46) noted the disappearance of calcium oxalate crystals from the urine of a patient given adequate amounts of hyaluronidase Prien (38) and others also reported that injection of hyaluronidase is followed by clearing of the urine Seifter (50) demonstrated that in rabbits hyaluronidase subcutaneously not only decreased the normally heavy turbidity of the urine but also caused a 50 per cent decrease in the sediment In sheep and cattle with renal calculi Puntriano (39) found that hyaluronidase cleared the urine and decreased the sediment Microscopically the effects were identical with those described in our earlier reports

In our experience the surface tension of urine is generally higher than normal in patients with renal lithiasis and the response to hyaluronidase is better in patients whose urine before treatment has a high surface tension than in those whose urinary surface tension is within normal limits The decrease in surface tension correlates closely with the clearing of turbidity and sediment when the latter were present initially Ravich (40-43) and Harlin and Wiesel (25) have recently reported similar results the latter obtaining a reduction of urinary surface tension after oral administration of glucuronic acid which is a breakdown product of hyaluronic acid

Table 1 gives the average results of surface tension determinations measured with the Du Nouy tensiometer and the pendant drop method in urine specimens from 960 subjects The figures clearly show that urinary surface tension varies with sex and race is influenced by pregnancy and that the surface tension of the urine of normal individuals differs significantly from that of urine of patients with renal stone

Since the tension varies considerably in the course of 24 hours

tensiometric determinations should be made at the same hour each day and under controlled conditions with respect to fluid and food intake temperature and the like

Electrophoretic determinations too reveal differences between the urine of normal individuals and those with renal calculi Unprotected colloidal particles have a pronounced electric charge as a result of the chemical unsaturation of the ions on their surfaces Particles completely protected by lyophilic colloids have at most only minute electric charge Thus centrifuged and noncentrifuged urine samples from normal persons exhibited practically no electrophoretic movement

TABLE 1—AVERAGE SURFACE TENSION VALUES OF 960 URINE SPECIMENS

SUBJECT TESTED			SURFACE TENSION DYNES/CM
Male			
	White	healthy	54
		renal stone	63
	Negro	healthy	48
		renal stone	51
Female			
	White	healthy	58
		renal stone	60
		pregnant no stone	54
	Negro	healthy	50
		renal stone	53
		pregnant, no stone	42

whereas samples from patients with renal calculi move to the positive pole indicating the strong negative charge of the colloidal particles

Boyce Garvey and Norfleet (9 24) recovered the nondiffusible colloidal components of the urine by a method combining dialysis ultrafiltration and evaporation By determining the electrophoretic mobilities of salts and colloids in the urine and the binding of histochemical dyes and inorganic ions they were able to demonstrate distinct differences between normal subjects and patients with calcium phosphate and/or oxalate calculi They came to the following conclusions *(1)* A soluble urinary mucoprotein (fraction 1) present in patients with calculous disease has electrophoretic mobilities at pH 8 6 and 4 5 thus differing from normal urinary mucoproteins *(2)* An insoluble carbohydrate or protein polymer present in the urine of normal subjects as well as of patients with calculi can be converted



PLATE 1.—Beginning of kidney stone formation in patient with rapidly forming bilateral calyceal calculi. Ultraphotomicrograph. Ultropak microscope.

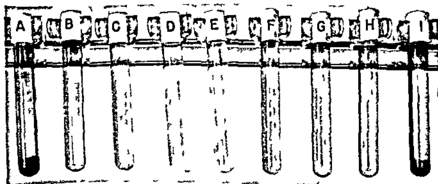


PLATE 2.—Effects of subcutaneous injection of 300 T.R. units of hyaluronidase on human urine. *A*, pretreatment. *E*, 3 hours after injection. *I*, 24 hours after injection.

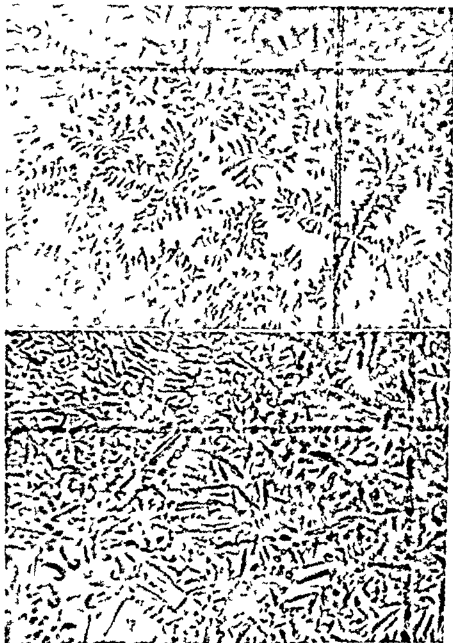


PLATE 3 (*above*)—Urinary sediment from patient before cortisone therapy

PLATE 4 (*below*)—Same patient urinary sediment at 24 hours after 100 mg of cortisone Note increased crystalluria and embryonal stone development Plates 3 and 4 ultraphotomicrographs Ultropak microscope

(depolymerized) to a soluble mucoprotein (fraction 2) by suspension in buffers of pH 12.3 (3) Calcium is bound by certain of these muco proteins and forms an insoluble complex with both fraction 1 and fraction 2 phosphate ions in the presence of this complex form free calcium phosphate crystals (4) Normal mucoprotein and fraction 2 mucoprotein do not increase nor promote crystal formation in the calcifying solution Apparently no infection was present in the pa tients observed in this study

The urinary pH too is important with regard to the precipitability of the urinary colloids Ultracentrifuge studies have shown that with increasing pH the urinary colloids are more apt to precipitate rap idly (7)

EFFECT OF URINARY TRACT INFECTION ON URINARY COLLOIDS

Some of the bacteria which cause urinary tract infections particu larly certain staphylococci and streptococci produce hyaluronidase In contrast to testicular hyaluronidase however the bacterial enzyme not only depolymerizes hyaluronic acid but continues the process down to end products of low molecular weight which have no ef fect as protective colloids. The presence of bacterial hyaluronidase particularly in a site over which urine passes results in degradation of the urinary hyaluronic acid and thus removes protective colloids This is why the introduction by catheter of any type of hyaluronidase into the urinary tract cannot be of benefit in renal calculous disease and may be extremely dangerous

Many organisms especially the pseudomonas, and some strepto cocci, staphylococci and Escherichiae also produce hyaluronic acid of considerably higher molecular weight than that normally excreted in the urine This acid is present in the bacterial capsule

Among our patients with upper urinary tract stone due to or com plicated by infection Ps aeruginosa was isolated in 28 per cent Twenty of the 21 strains isolated were vigorous producers of high molecular weight hyaluronic acid The latter acid has a marked pre cipitating and gluing effect instead of a protective colloid effect It was found that purification and dissociation of the crude hyaluronic acid from the other bacterial substances first decreased the precipitat ing effect and finally gave it protective colloid properties Possibly therefore the molecular size of the hyaluronate may be graded down

during purification The protein fraction attached to hyaluronic acid can discharge colloidal systems which may also influence the physico chemical properties of the urine

Seifter and Baeder (52) found that highly polymerized hyaluronic acid obtained from Str pyogenes bovine vitreous humor and human umbilical cord has no significant spreading action Partially depoly merized streptococcic hyaluronic acid has a marked spreading effect in experimental animals but further depolymerization results in prod ucts with practically no spreading action

In a small group of patients with infections that had become com pletely resistant to antibacterial agents parenteral administration of hyaluronidase seemed to increase the effectiveness of the antibiotic Possibly the exogenous hyaluronidase results in the release into the urine of a hyaluronic acid which acts as a dispersing and peptizing agent thereby sensitizing the bacteria to the action of the antibiotic Other workers too have noted that prolonged administration of hyaluronidase alone eradicated infection that had proved refractory to other treatment (21 49)

GROUND SUBSTANCE DISTURBANCE AND CALCULUS FORMATION

It has been repeatedly demonstrated that hyaluronidase attacks the intercellular ground substance and that ACTH cortisone and stress oppose this action It therefore seemed worth determining whether the adrenal steroids administered or released by stress would affect the urine and minimize or nullify the beneficial effect of hyaluronidase Were this the case urolithiasis might prove to be another manifestation of disordered function of the ground sub stance (12 19 20)

The mesenchymal ground substance is composed of about 20 known substances of which the most thoroughly investigated and best understood is the mucopolysaccharide hyaluronic acid Adminis tration of hyaluronidase releases hyaluronic acid at the site of in jection as the effect of the enzyme decreases the ground substance begins to reconstitute itself The excess hyaluronic acid or substrate appears in the blood soon after administration of the enzyme and during the period of repair Thus this acid which is an excellent protective colloid is excreted into the urine Cortisone by blocking

hyaluronidase action inhibits or slows the release of hyaluronic acid into the urine (51) Desoxycorticosterone acetate (DCA) on the other hand has the same effect on hyaluronic acid as hyaluronidase *The effect of ACTH or stress on the intercellular ground substance* resembles that of cortisone there is an active breakdown of nucleo protein and increased excretion of phosphate and uric acid Further more stress like administered ACTH or cortisone "freezes" or prevents depolymerization of the ground substance and thus de creases the urinary protective colloids

Administration of cortisone or ACTH is followed by a marked decrease in the urinary excretion of glucuronic acid and glucosamine which would seem to indicate a decreased urinary output of hyalu ronic acid When hyaluronidase therapy is planned it must be borne in mind that concurrent ACTH or cortisone administration nullifies the effect of hyaluronidase by blocking the action of the enzyme upon its substrate hyaluronic acid (51)

The observation in a large series of patients that intense or sus tained emotional stress resulted in increased urinary turbidity due to phosphates or urates led to a study in which the effect of stress could be evaluated more critically In this experiment 6 individuals were subjected to stress in the form of simulated high altitudes in the compression chamber and accelerations of 3½ to 5 G by centri fuging The urinary cloudiness and sedimentation increased in 3 of the subjects Chemical analysis of blood and urine during the experi mental period showed that the increase could not be explained on the basis of an appreciable shift in pH *The decreased solubility* and dispersion were due to a relative decrease in protective colloids as revealed by the ultramicroscope during and immediately after the periods of stress The urine also became darker the reverse of the effect of optimal doses of hyaluronidase

Urolithiasis does not develop in Addison s disease judging from a collected series of patients with this disease In contrast renal calculi often occur in Cushing s syndrome The hypercalcuria, which is a frequent manifestation in the latter condition is probably not the sole factor *responsible for the common occurrence of calculi* In 1 of our patients there seemed to be direct evidence that cortisone by re ducing the protective urinary colloids is a factor in the calculogenesis in Addison s disease This patient, after 13 years of DCA therapy was given cortisone within 6 months the level of urinary colloids dropped

and calculi developed in both kidneys Withdrawal of cortisone and renewed DCA therapy has been followed by a 26 month period without growth of renal calculi

Urinary surface tension is low in Addison s disease and high both in Cushing s syndrome and after administration of cortisone (25) This seems to indicate that a change of the urinary colloids has taken place which affects surface activity

Rabbit urine usually contains a large amount of sediment Bilateral adrenalectomy like hyaluronidase administration decreases the amount of sediment (53) In other experiments it was found that the effects of bilateral adrenalectomy and hyaluronidase are additive

In 8 of 12 patients receiving cortisone the urine became cloudy and the sediment increased this was not accompanied by a change in urinary pH A striking crystalluria shown by ultramicroscopic study indicated the suppression of urinary colloids (Plates 3 and 4) Even relatively small doses (25 to 50 mg every 6 hours) have this effect within 6–12 hours (12 19 20) Hyaluronidase administered during cortisone therapy will not clear turbid urine and increased incrustation on indwelling catheters has been noted following prolonged cortisone therapy (4) In 2 of our patients on cortisone therapy renal colic developed due to formation and passage of uric acid calculi in neither was the level of the blood uric acid elevated and in both there was a 50 per cent reduction of the protective colloids during cortisone therapy Baker (4) has reported 8 cases of uric acid calculi (3 renal 5 bladder) after prolonged administration of cortisone only 3 of the patients had an elevated serum uric acid level

In the Dalmatian dog, ACTH produced a threefold increase in uric acid excretion as well as aggregation of uric acid crystals without formation of true calculi (47) The same investigator also reported that he had found large numbers of uric acid stones in persons under unusual conditions which presumably represented a state of stress

From my own experience and that of other military surgeons clinical evidence seems to indicate that battle stress may predispose to stone formation A much higher incidence of nonopaque ureteral calculi was noted among men subjected to enemy fire than among troops at the rear Environmental conditions climate food and water were the same for both groups the only difference was the relative safety and lack of severe emotional and physical stress in the latter group The incidence of stone among the young inexperienced men under actual

combat conditions is higher than among seasoned experienced troops according to Kimbrough (31) Animals subjected to severe stress had a higher incidence of uric acid calculi than control animals (47)

A recent study by Baker and associates (5) would seem to show that renal calcification induced by parathyroid hormone may be due only in part to the effect of the hormone on calcium levels in the serum and urine apparently the state of the renal connective tissue plays a vital role Change in the condition of the ground substance by means of toluidine blue or DCA, or as a result of renal hypertrophy they found increases or decreases nephrocalcinosis The results of these studies seem to confirm Engel s (22) hypothesis that parathyroid hormone acts directly on ground substance Certain analogies can be found in Albright s (1) observation that parathyroid hormone has a direct effect on the renal tubules Calcification within the ground substance of connective tissue is apparently closely related to the state of the connective tissue as influenced by the hormone Further study by Baker and Sison (6) has shown that a common mechanism i.e the striking influence of hyper or hypoadrenocorticism on ground sub stance influenced experimental renal calcification produced by oxa mide irradiated ergosterol and estrogen-androgen imbalance

HYALURONIDASE THERAPY

General Considerations

Hyaluronidase therapy for renal lithiasis should be considered when *(1)* renal function is adequate as determined by the excretion of contrast mediums used for excretory urography and by phenol sulfonphthalein excretion *(2)* a trial injection is followed by signifi cant clearing or turbidity and decrease of sediment (when present) and *(3)* a reduction in urinary surface tension to normal or below normal range The usual clinical laboratory and roentgenographic procedures for investigating patients with calculi should be performed Cystoscopic examination and retrograde pyelography should be omit ted if all the necessary information can be obtained without these measures Results of urinary colloid estimations may be inaccurate if there is bleeding and exudate formation

The effect of hyaluronidase therapy may be conveniently followed in a series of noncentrifuged urine specimens Samples should be

taken before and during therapy and allowed to settle for 1 hour at room temperature The turbidity and sediment usually begin to diminish in urine voided about 30 minutes after the first injection (Plate 2) If turbidity and sediment increase in successive 4 hour specimens another dose of hyaluronidase should be given if this does not decrease the turbidity and sediment the dose should be increased In addition the response to therapy may also be observed by comparing the rate at which deposits form on the glass tip attached to the indwelling catheter draining the urinary tract during periods with and without the enzyme therapy Such deposits form markedly in nephrostomy drainage tubes and are least pronounced in bladder catheters

Urinary surface tension should be determined with the Du Nouy tensiometer when the urine is initially clear and free of sediment It should also be used for determination of the correlation between reduction in surface tension and decrease in turbidity and sediment Surface tension decreases from 6 to 8 dynes per centimeter within 30 minutes to 2 hours after a sufficient dose of hyaluronidase and remains at this level so long as the enzyme maintains its effect

For injection the lyophilized hyaluronidase is reconstituted under aseptic conditions by adding 10 or 5 cc of sterile saline solution to a vial containing 1 500 turbidity reducing units (T R units) of the enzyme This provides a solution containing 150 or 300 T R units per cubic centimeter respectively the stronger solution is convenient when larger doses are required When prepared under strict asepsis the solutions are stable without refrigeration for 2 weeks If other standardized units are used to indicate the strength of the hyaluronidase recalculation is necessary for example 500 viscosity units is approximately equal to 150 T R units The enzyme is injected subcutaneously with a 25 gage 3/8 in needle the site of injection should be changed constantly Local infection may develop during self administration the infected site should of course be avoided for any further injection

The dose required to clarify cloudy urine or cause a significant reduction in surface tension varies widely from patient to patient and must therefore be individually determined (12 19 20) Patients whose urine is initially clear and with surface tension above normal levels need smaller doses In such cases the test dose begins at 150 to 300 T R units and is increased until a favorable response is obtained or

until it becomes evident that no such response is forthcoming Since many infections increase the requirement for hyaluronidase test doses of 300 to 450 T R units should be used for these cases therapeutic doses of 600 to 900 T R units every 12 to 24 hours may be necessary

Poor renal function and hypersensitivity to hyaluronidase are contraindications to therapy Practically no allergic reactions were produced in our studies with the highly purified enzyme marked urticaria developed in 4 of 960 patients given hyaluronidase but all were later given the enzyme without adverse reaction In view of this almost total lack of sensitivity no desensitization has been tried

Early in our investigation it became apparent that inadequate doses of hyaluronidase may increase the tendency for precipitates of urinary crystals to form so that growth of calculi is accelerated (16 38) If the stones are small and attached to a calyx accelerated growth may result in their becoming dislodged and passed Thus in 1 patient with multiple small calyceal calculi bilaterally in whom 300 T R units daily had controlled the formation growth and passage of stones for 2 years a sensitizing dose of 15 units was followed the next day by the passage of 3 small stones Presumably the small dose of enzyme had caused a rapid growth and subsequent detachment of calyceal stones Proper dosage thereafter again controlled the calculogenesis and passage of stones

Hauser (16) suggests that this phenomenon may be due to a "sensitization reaction" Urine examined with the Ultropak microscope after administration of inadequate doses of the enzyme revealed much more rapid aggregation of crystalloids than before the start of therapy Prien (38) observed in a patient with cystine calculosis that a stone removed before therapy had been started consisted as usually of a loose collection of hexagonal platelike crystals A stone removed during therapy was composed of closely packed microscopic needle like crystals (spherulites) Spherulitic growth according to Prien is common when a foreign material is present in the crystallizing solution which interferes with the development of the growing crystals

If the urine does not clear and urinary surface tension is not significantly reduced after 6 to 8 hours hyaluronidase treatment should not be instituted The hyaluronidase effect can be determined in any physician s office or laboratory Not infrequently the dose must be adjusted on the basis of follow up tests In our patients we arbitrarily try to keep the urine clear for 16 to 24 hours after a single injection

Occasionally two injections a day are necessary, particularly in post operative patients It has not yet been established whether and when hyaluronidase therapy may be discontinued In the presence of ready calculogenesis therapy may possibly have to be continued indefinitely

Prolonged use of hyaluronidase has caused no recognizable histo pathologic lesions or noticeable metabolic changes Even large doses (600 to 900 T R units daily) for 2 to 3 years have not produced any change in calcium phosphorus sodium, potassium chloride or water excretion Within the time span of our study no major difficulty has developed which might be attributed directly to the treatment when the dosage was correct

Any long continued therapeutic regimen requires the fullest co operation from the patient As in diabetes mellitus the patient with renal calculi must be made to understand the nature of his disease and thus the reasons for the treatment Obviously the need for almost daily injections and the cost of long continued treatment become bur densome But careful clear explanation by the physician can accom plish a great deal in maintaining a co operative attitude in the patient

Calculosis is a constitutional as well as a local disease and the treat ment of severe calculous diseases demands day to day control Every measure which may help to minimize the formation growth or re currence of stone should be employed Hyaluronidase therapy must be considered an adjuvant to all the usual forms of treatment If metabolic disorders are present appropriate measures for their control are indicated The pH of the urine should be adjusted by diet and medication to facilitate solution of critical urinary components For phosphatic stone 1 oz of basic aluminum gel or 1 Gm of dihydroxyl aluminum aminoacetate is prescribed to be taken after each meal and at bedtime Diet is important and fluid intake should be large enough to maintain a daily output of 3 000 cc of urine Vitamin A 50 000 units daily should be administered Urinary tract obstruction if present should be corrected by appropriate measures Urine cultures should be done routinely to detect the possible presence and type of infection and sensitivity tests are advisable so that antibiotics may be used most effectively

Clinical Experience

In the period from September 1950 to July 1954 a series of 642 patients with calculi of the upper urinary tract was carefully followed

A group of 59 patients from this series was selected for hyaluronidase therapy on the basis of the following criteria (1) a marked tendency to formation of renal calculi (malignant calculogenesis) (2) conditions tending to enhance the rate of stone growth (3) failure of previous treatment to control the formation and growth of calculi and (4) possibility of a favorable response to hyaluronidase as indicated by laboratory determinations

Of the 59 patients so selected 44 have been under treatment for periods ranging from 30 to 47 months or an average of 33 months 23 of the patients had previously undergone one or more operations for stone and 11 of the operations were nephrectomies The ages ranged from 17 to 79 years All the patients were white 24 of them were men 20 were women

All the patients have been closely followed by laboratory tests and by roentgenography every 60 to 90 days As control we used the clinical course of the patients before the start of the enzyme therapy although it was fully realized that this is not necessarily a completely reliable means for comparison In many cases it was difficult to estimate the time interval between the first knowledge that a stone was present and beginning of any treatment Furthermore there were fewer agents—chemotherapeutic and antibiotic—available in the pretreatment period Most of the patients in the group followed the prescribed regimen reasonably well although this is not a strictly objective conclusion On their own initiative 4 patients in whom stone formation was under control discontinued treatment for 3 5 7 and 8 months respectively upon withdrawal of the enzyme the stones rapidly increased in size

An additional 21 patients who underwent renal surgery requiring catheter drainage were given hyaluronidase pre and postoperatively In 17 of them the catheters showed noticeably less calcareous deposits during therapy than during the control period without hyaluronidase

On the basis of earlier observations regarding the response to hyaluronidase therapy the 44 patients were divided into 2 groups Group A consisted of 20 patients with multiple small calyceal or other small calculi which formed and passed rapidly from one or both kidneys From the history and the laboratory and roentgenographic findings the stones in this group were considered to be primary Group B consisted of 24 patients with large stone or stones and multiple small stones in one or both kidneys These were considered to be of second

ary type or secondary stones superimposed on a primary stone as nucleus

Results were graded as follows (1) control of stone formation or growth no passage of stone (2) reduced rate of stone development and growth as compared to previous status of calculogenesis (3) de creased size and density of stone (4) no arrest or retardation of de velopment growth or passage of stone (Table 2) The last category also included 3 patients in whom the development growth or passage of stone was accelerated after therapy presumably because inadequate doses of hyaluronidase sensitized urinary crystalloids

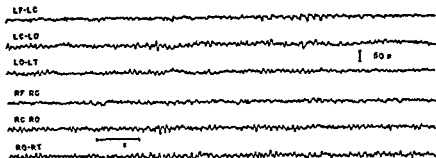
GROUP A —Stones from 14 patients were available for analysis 12 stones were composed of calcium oxalate and calcium phosphate 1

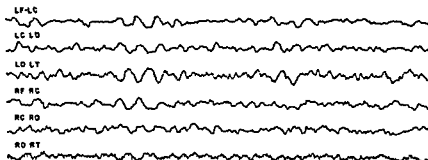
TABLE 2 —RESULTS OF HYALURONIDASE THERAPY OF RENAL LITHIASIS

GROUP	FORMATION OF CALCULI CONTROLLED	FORMATION OF CALCULI REDUCED	CALCULI SMALLER OR LESS DENSE	FORMATION OF CALCULI NOT CONTROLLED
A (20 cases)	12	4	1	3
B (24 cases)	8	7	2	7

of cystine and 1 of uric acid Urine cultures at the start of the study were negative in 12 patients later a secondary Esch coli infection *developed in 1 patient and a Staph aureus infection in another*

Among the patients in this group were members of a family with cystinuria 3 of these patients have calculi in both kidneys 2 of them large stones in each kidney and 1 multiple small stones in both kid neys It is noteworthy that the 2 members of the family with cystinu ria but without stones excrete adequate amounts of protective urinary colloids There was no deficiency of protective urinary colloids in the 2 with large calculi whereas in the 1 with small stones the deficiency was marked on this basis only the latter was placed in group A All 3 patients had been treated elsewhere for a number of years by the usual medical management of cystine lithiasis despite the rigid treat ment gradual growth of the large stones continued in 1 patient and small calculi continued to form and pass in another patient at rather frequent intervals With the start of enzyme therapy the patients were put on an unrestricted diet and alkalinizing drugs were stopped Hyaluronidase had no effect in the patient who had been refractory to medical management the patient with large stones fairly well controlled previously was again controlled by the enzyme in the





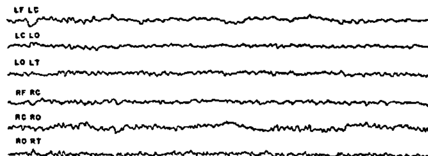


Fig 1.—Serial electroencephalograms of a patient in whom impending hepatic coma was induced by oral administration of ammonium salt. *Top* and *bottom* series the patient without clinical signs of impending coma *center* record when mental confusion and the "flapping" tremor were marked (34)

dorsiflexed Before the tremor itself appears an irregular lateral movement of the fingers may sometimes be visible The same type of tremor or arrhythmic muscle movement may be observed upon dorsi flexion of the foot forcible closing of the eyes pursing the lips and the like A detailed description and definition of this tremor is given by Adams and Foley (2) Occasionally, a patient may progress into typical hepatic coma without exhibiting this characteristic tremor at any time In patients who recover temporarily or permanently the tremor gradually disappears although it may persist continuously or at irregular intervals for many weeks or even months It is usually the earliest and one of the most characteristic signs of impending hepatic coma When the syndrome progresses to deep coma the extremities usually become flaccid and the tremor disappears in fact to elicit the tremor some muscle tone is necessary At times it may be possible to elicit the tremor even in the comatose patient by passive flexion and extension of the wrist or elbow if resistance to this motion occurs the tremor will resemble cogwheel rigidity except for its irregularity and the lack of established rhythm Occasionally this characteristic tremor has been observed in severe chronic pulmonary disease in cor pulmonale in bromidism, and in a few other disturbances not related to primary hepatic disease

The encephalographic disturbances (Fig 1) were first described by Foley Watson and Adams (19) and described as follows Paroxysms of bilaterally synchronous symmetrical high voltage slow waves in the delta region of 1 5 to 3 per second interspersed with or superimposed on relatively normal (alpha) waves" With these slow waves bursts in the frontal region usually appear early in impending coma spreading over the entire record as the syndrome progresses These characteristic changes often disappear in deep coma and in a few patients the phenomenon does not appear at any stage although in other respects the progress of events is typical The same changes may be observed occasionally in electroencephalograms of patients with uremia and hypokalemia

The stage of impending hepatic coma may last from a few hours to many days or even weeks In 1 patient bouts of impending coma lasting a few days to a week or so have been observed at frequent intervals for almost 2 years Generally however a few days will suffice to usher in stupor and deep coma Occasionally the change from impending coma to deep coma and vice versa may occur in an

hour or less For example a patient may be quite conscious in the morning, comatose an hour later and again quite normal in the after noon The reasons for the variations in rate of change in the state of consciousness are quite unknown In the typical patient, the process moves gradually to stupor and finally coma so that the patient cannot be aroused The coma itself varies considerably in depth When the coma is light the patients may respond to stimuli with movement of the extremities a grimace or even an audible sound Reflexes are usually present in the earlier stages of coma and may at times be hyperactive even asymmetrically so Babinski s sign may sometimes be present transiently In deep coma there may be areflexia (includ ing the corneal reflexes) Convulsions have been uncommon in our series of patients with hepatic coma although Adams and Foley found that about a third of their patients had a convulsion usually near the fatal termination

The comatose state may last from several hours to a week or two the most frequent duration being about a week

The prognosis for a patient with hepatic coma is extremely grave Once clear cut evidence of impending hepatic coma has appeared death is extremely likely nevertheless we have observed a small group of patients with typical impending coma who recovered and subsequently showed evidence of improved liver function With the appearance of deep coma the prognosis becomes even poorer Al though the patient may awaken the improvement is usually transient and he soon lapses back into coma which ends fatally

PATHOGENESIS

The cause of hepatic coma is not known Nevertheless several pre disposing factors have been recognized and with increasing knowl edge more instances are recorded in which one or more of these factors may be found to explain the onset of coma Understanding of the exact manner in which these factors operate must wait until there is better knowledge of the existing metabolic abnormalities It is also not known whether these factors actually initiate a chain of events leading to hepatic coma or whether they merely accelerate a process already begun or inevitable The following may be used as a working hypothesis In the presence of liver disease metabolic abnormalities exist which if severe enough prevent the organism from carrying

certain metabolic loads The precipitating factors would impose a metabolic load on the liver with which it is no longer able to cope The genesis of hepatic coma would therefore depend upon the severity of the liver disease and the load which the liver must carry

Perhaps the most frequent precipitating factors are (1) injudicious use of sedatives (2) acute infections (e g pneumonia peritonitis bacteremia) (3) major surgical procedures (4) abdominal paracentesis and (5) gastrointestinal bleeding especially that due to gastritis duodenal ulcer or esophageal varices (40)

Patients with severe liver disease tolerate poorly most sedatives and analgesics with a prolonged action In susceptible patients these drugs act as precipitating factors for coma The worst offenders are morphine and its derivatives and paraldehyde presumably because most of these alkaloids are either metabolized or excreted by the liver so that in the presence of severe liver damage are not well handled The longer acting barbiturates especially barbital and as an analgesic demerol are the agents of choice but even these substances may occasionally be implicated in the genesis of the syndrome Modern therapeutics including the use of antibiotics to combat infection and repeated blood transfusions when there is bleeding have reduced the incidence of infection and the occurrence of shock Whether these measures have actually altered the prognosis is not known it seems likely however that while they may not have permanently reversed the comatose state in many patients they may have prevented it from occurring in others and allowed recovery with regeneration of hepatic tissue to occur

An understanding of the pathogenesis of hepatic coma depends upon better knowledge of the metabolic relationships between liver and brain and the metabolic disturbances in severe hepatic disease Little is known as yet, about these factors although a beginning has been made by defining some of the metabolic abnormalities in hepatic coma and relating them at least on a theoretic basis to a picture of the pathogenesis of the condition It seems probable that until these metabolic relationships are understood more clearly no intelligible concept of the pathogenesis of hepatic coma will be forthcoming It is germane here to discuss the metabolic abnormalities of hepatic coma in relation to the biochemistry of liver and brain function and to attempt to provide one or more hypotheses to explain the condition So far as possible certain of the constituents in the metabolic pool will be considered individually although it is well recognized that the inter

relationships between these individual nutrients are extremely varied and numerous

WATER AND ELECTROLYTE METABOLISM —An upset in renal function usually but not always occurs at some time during hepatic coma and

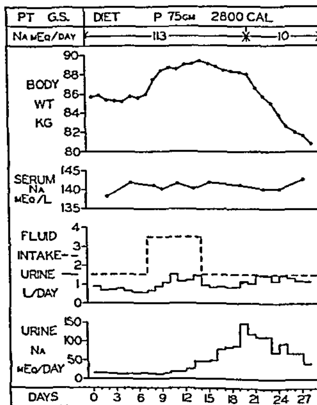


FIG 2.—Failure of a patient with severe cirrhosis to excrete a water load. Hyponatremia was not produced in this instance and a moderate sodium and water diuresis is evident

is most prominent when the coma is deep The dominant change is an oliguria despite normal, or in some instances excessive hydration Patients with liver disease without any sign of mental confusion regularly exhibit abnormalities in water metabolism Thus an expansion of plasma volume has been shown to occur in viral hepatitis (27) In many patients with cirrhosis a delayed water excretion commonly results in oliguria during the day and in excessive urination at night

the water retention is usually not so severe as to lead by itself to ascites or edema formation Presumably, such delayed water excretion is due largely to increased activity of posterior pituitary antidiuretic hormone (ADH) either because of impaired ADH metabolism (35)

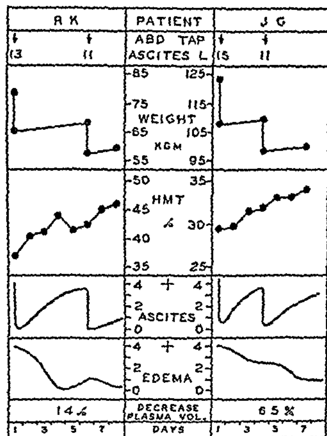


Fig 3 —Changes in body weight and hematocrit following paracentesis of two patients with stabilized cirrhosis

or from increased secretion as a physiologic response to reduced plasma volume during ascites formation (21) Studies of renal plasma flow and of glomerular filtration have so far not revealed a sufficient reduction from the normal to account for this delayed water excretion It has not been established whether the oliguria of hepatic coma (Fig 2) represents a striking increase in ADH activity or whether it is due to changes in renal hemodynamics The latter concept would

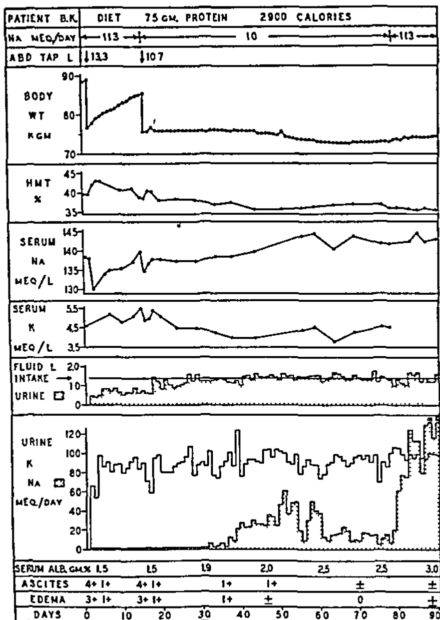


Fig 4—Failure of a patient with chronic stabilized cirrhosis to excrete ingested sodium while forming ascites Subsequently sodium and water diuresis rise in serum sodium concentration, and fall in hematocrit occurred while patient was maintained on a sodium restricted diet, after which he was able to excrete the sodium load (21)

seem to be supported by the decrease in blood pressure which is occasionally marked Oliguria frequently occurs during the first 24 to 72 hours after paracentesis presumably because this procedure is a dehydrating phenomenon being associated with a rising hematocrit value (Fig 3) In this circumstance a reduction in renal plasma flow and in glomerular filtration can be expected to occur The same may be said with regard to major surgical procedures in which increased ADH activity is now fairly well documented The oliguria which some times occurs when the hepatic coma is related to other precipitating factors or appears spontaneously has not yet been explained

Sodium excretion is greatly reduced in patients with cirrhosis in whom ascites is forming so that regardless of intake no more than 1 to 5 mEq of sodium per day are usually excreted in the urine (16) (Fig 4) It has been assumed that this sodium retention is caused by an increased activity of the adrenal sodium-retaining hormone caused as with ADH by failure of the liver to metabolize this hormone nor mally or appearing as a response to dehydration and a lowered plas ma volume (21) As a rule no particular change in excretion occurs when coma sets in the retention already being almost complete The control of ascites and edema formation demands severe dietary re striction of sodium—approximately 200 mg per day (15 12) When sodium is thus restricted in the presence of marked oliguria a high fluid intake will inevitably be followed by overhydration and a reduc tion in serum concentration of sodium This has actually been ob served in a number of patients in whom overzealous fluid therapy without sodium was administered in the face of a persistent oliguria Whether this represents a true sodium depletion syndrome or water intoxication is not entirely clear Nevertheless occasionally a patient who is drowsy or even in coma and whose serum sodium concentra tion is extremely low has responded to the administration of hyper tonic saline solution by an improved state of consciousness Although massive ascites and edema call for sodium restriction in spite of a reduced serum sodium concentration the appearance of coma or of impending coma is of such grave import that sufficient sodium must be administered The reasons for these alterations in the state of consciousness due to shifts in sodium and water are not known Pre sumably some change in brain metabolism occurs

The serum potassium concentration in hepatic coma may be ele vated but more commonly is normal or reduced (4 37) (Table 1)

The appearance of hyperkalemia is usually the result of diminished renal function and is roughly proportional to a rising concentration of nonprotein nitrogen in the blood which occurs when oliguria is pronounced No clear etiologic relationship between hypokalemia and the

TABLE 1 —SERUM POTASSIUM CONCENTRATION IN HEPATIC COMA

	PATIENT	K mEQ./L.
Impending coma		
	1	3 4
	2	4 0
	3	3 6
	4	3 0
	5	5 1
	6	3 5
	7	4.2
	8	2 5
	9	2 8
	10	3 2
	11	4 5
	12	3 6
	13	5 9
	14	3 8
	15	3 3
Coma		
	1	2 8
	2	4 0
	3	2 8
	4	5 0
	5	2 6
	6	3 5
	7	4 2
	8	3 8
	9	
	10	7 0
	11	3 9
	12	5 2
	13	3 1

Mod fied f m Schwartz *et al* (37)

appearance of coma has so far been found The administration of potassium salts by mouth or parenterally will usually correct the hypokalemia when it is present but has not, at least in our hands affected the state of consciousness. Occasionally in patients with severe liver disease profound hypokalemia may develop from known causes *e g* depletion by exchange resins In such cases hyperreflexia and even

loss of consciousness may occur and does respond as in other instances of severe hypokalemia to reversal of the potassium depletion

CARBOHYDRATE METABOLISM—Although abnormal results of the glucose tolerance test are sometimes observed in severe cirrhosis they are unusual and, with the crude measurements available, it may be said that glucose disappearance is usually normal or not far from it (9) The same is true in hepatic coma although few studies have been completed Hypoglycemia is observed only rarely and is then usually associated with massive necrosis or atrophy This is not true of the blood pyruvic and lactic acids concentrations Snell and Butt (41) reported a high blood concentration of pyruvic and lactic acids in hepatic coma and Amatuzio *et al* (3) found a progressive rise in pyruvic acid after glucose administration not noted in conscious patients with severe liver disease These observations suggest that the defect in carbohydrate metabolism in hepatic coma is at the level of pyruvic acid utilization rather than due to a failure in the breakdown of glucose to pyruvic acid In some respects this metabolic abnormality resembles that found in severe thiamine deficiency (beriberi) but a true exogenous thiamine deficiency seems unlikely in hepatic coma as most of these patients are given large quantities of thiamine as well as other vitamins However it is possible that thiamine is not converted in usual amounts to cocarboxylase (thiamine pyrophosphate) a phenomenon observed by Williams and Bissell (49) in chronic cirrhosis The functioning of the citric acid cycle has not been studied in hepatic coma

PROTEIN METABOLISM—The intermediary metabolism of protein has been more carefully studied although we still seem to be only scratching the surface The blood amino acid content may be elevated under certain circumstances in severe liver disease the chief being widespread or massive liver necrosis In this condition the dying liver cells presumably furnish the body with large quantities of a "liver hydrolysate or "autolysate and the almost complete lack of liver cells leads to the failure of deamination of amino acids as it does in the hepatectomized animal Except in such cases and particularly when the liver disease is stabilized hepatic coma does not lead to aminoacidemia and when it does the rise is usually slight (30 45) Aminoaciduria is frequently present in cirrhosis but is not excessive when measured as total alpha amino nitrogen or as individual amino acids (Fig 5)

Ammonia is formed when amino acids are deaminized which occurs

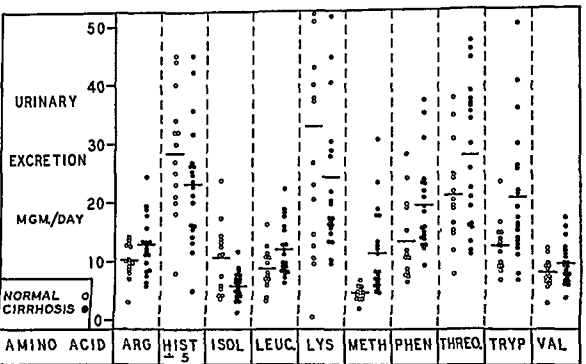


FIG 5—Urinary retention of amino acids in normal subjects and in patients with cirrhosis (20a)

chiefly in the liver and in the intestine as a result of bacterial action Ammonia is a highly toxic substance which normally is present in the blood in slight, if any amount being combined with alpha ketoglutaric acid to form glutamic acid with glutamic acid to form glutamine or made into urea (Fig 6) Glutamine is considered by some investigators to be a sort of "storage substance for ammonia more being formed when ammonia is produced in excess Usually the bulk of formed ammonia is converted to urea a process confined to the liver Krebs and Henseleit (25) presented conclusive in vitro evidence that only

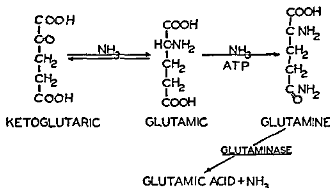


FIG 6—Relation of ammonia to glutamic acid and glutamine formation (Chart constructed by Dr J E Seegmiller)

liver tissue forms urea from ammonium salts The work of Bollmann Mann, and Magath (6) had previously defined the liver s role in the deamination of amino acids and the formation of urea from ammonia in hepatectomized dogs A high concentration of ammonia develops in the blood of the hepatectomized animal and if blood glucose concentration is maintained the animal dies with emesis lethargy and convulsions It is not surprising therefore that ammonia should be implicated in the genesis of hepatic coma Monguio and Krause (29) suggested this in 1934 after finding that dogs with liver injury or an Eck fistula when fed meat, had a high blood ammonia concentration In fact, they proposed that patients with severe liver damage be given only small amounts of protein food a concept that has been revived recently Fuld (20) in 1933 observed somewhat elevated blood am

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Presumably most, if not all of the ammonia in the body is present as ammonium ion (NH_4)

monia concentrations in patients with liver disease and at about the same time van Caulaert and colleagues (43) reported that in addition to the frequent presence of a high blood ammonium concentration in certain diseases of the liver a disturbance of the central nervous system could be induced in patients with Laennec s cirrhosis by the admin istration of ammonium salts Kirk (24) also made an extensive study of ammonium metabolism in liver disease particularly hepatitis

Recently with a better definition of impending hepatic coma and its relation to deep coma it has been possible to induce this syndrome by the administration of ammonium salts to patients with cirrhosis (34) and in a patient with an Eck fistula (28) Ammonium chloride not only induces the typical state of impending hepatic coma in such patients but its administration when inadvertently continued may also cause deep and irreversible coma Nitrogenous substances—diammonium citrate urea, and an increase in food protein—also produce this syndrome in some patients (34) Kirk (24) felt that some of the phenomena following ammonium ingestion could be ascribed to acidosis but the occurrence of the same syndrome in patients given nitrogenous substances makes it unlikely that acidosis is an important pathogenetic factor So too does the finding of a usually normal or only moderately reduced blood bicarbonate content and blood pH (37) It should be emphasized that by no means in all patients with severe liver disease will the syndrome develop following ingestion of these materials even when it is prolonged and large quantities are given Moreover the impending coma induced by administration of ammonium chloride or the other substances was rapidly reversed when the offending substances were discontinued Presumably the urea and protein were not injurious in themselves but were changed to am monia in the gastrointestinal tract by urease and deaminase activity

The blood ammonia concentration has been measured by several methods and by comparing normal individuals with patients suffering from spontaneous or induced impending hepatic coma or from spon taneous deep coma The methods usually have depended upon the microdistillation of ammonia from blood That devised by Seligson (39) and modified somewhat by others (38) involves the distillation of ammonia from the blood in a small closed bottle onto a glass rod moistened with phosphoric acid After a stated time interval the rod is removed dipped into Nessler s solution and the color formed is read against a standard in a colorimeter The method devised by Con

way and Burne (11) utilizes the porcelain dishes designed by Conway for the distillation of ammonia from one chamber to the other from slightly alkalinized blood into acid which is then titrated using micro burets The latter method was used by Traeger *et al* (42) and has been well standardized by McDermott and Adams (28) using boric acid as the ammonia receiver and titrating with 0 003 N hydrochloric acid By both of these methods ammonia is liberated from the blood at first rapidly but later slowly so that by the end of an hour a plateau is reached How much of this ammonia is from free ammonia (ammonium ion) in the blood and how much is derived from the several possible substances having labile ammonium radicals is not known It seems most likely that the existing free ammonia is rapidly distilled during the first few minutes and that the subsequent slow release of ammonia may well be from other materials Many of the in vestigators using these methods distill for only 10 or 15 minutes and assume that this represents "free ammonia Depending upon the many technical details followed by various authors a wide variety of normal and abnormal blood ammonia values have been recorded in the literature Which of these is the most accurate and most truly repre sents blood ammonia (if it exists at all in the blood normally) must await further investigation of the methods

In spite of these difficulties many patients with cirrhosis of the liver do have a somewhat elevated blood ammonia content and most pa tients with hepatic coma in its various stages will have an even higher value (Fig 7) In the hands of most investigators however the blood ammonia content has not accurately paralleled the state of the pa tients consciousness (37 38 42) Whether this lack of complete cor relation arises from an error in methods and would be improved if tissue instead of blood were studied or whether ammonia is not the toxic substance inducing liver coma cannot be stated at present It is possible that ammonia produced in the body or absorbed by the gastro intestinal tract is converted into some other closely related substance even more toxic than ammonia itself This concept is substantiated to some extent by the frequent presence of fetor hepaticus in pa tients with severe liver disease especially in hepatic coma The odoriferous substance may possibly be an amine in fact this sign has been known for many years as amine breath

There seems little doubt that ammonia or some closely related sub stance is toxic to patients with severe liver disease under some of the circumstances outlined above Just how the ammonia acts is not under

stood although Weil Malherbe (48) found that ammonium ions in crease the aerobic glycolysis and inhibit the anaerobic glycolysis of brain slices It is certainly a powerful metabolic poison both in vivo and in vitro Its precise relation to the mental confusion tremor elec

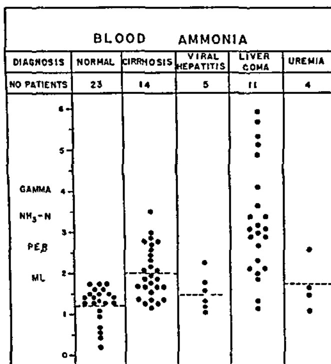


Fig 7—Blood ammonia content in cirrhosis and other conditions measured by the Conway technic (42)

troencephalographic changes coma disturbance in water and electro lyte metabolism and other clinical phenomena associated with hepatic coma requires much further investigation

The blood glutamine concentration measured by the specific de aminase activity of Clostridium perfringens did not parallel the clini cal manifestations of hepatic coma (Fig 8) in the hands of Seegmiller and co workers (38) although Flock *et al* (18) found a high gluta mine content in the brain after hepatectomy in dogs and Walshe (44) observed increased urinary excretion of glutamine of patients with hepatic coma Brain slices are able to form glutamine from glutamic

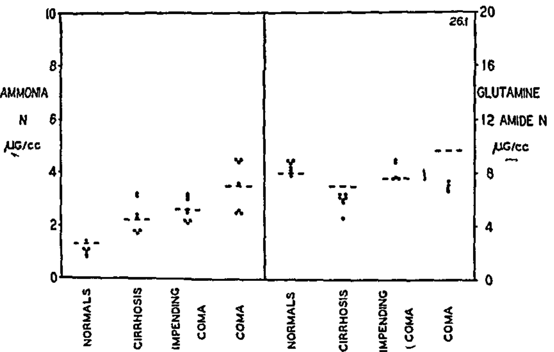


FIG 8 —Plasma ammonia and glutamine content in normal subjects and in patients with cirrhosis (38)

acid and ammonia (26), particularly in the presence of glucose with pyruvate or ketoglutarate (48) These reactions which remove ammonia have been considered "ammonia binding mechanisms" and have led to the administration of glutamate to patients with hepatic coma

FAT METABOLISM —Although the liver is extremely important in the metabolism of fat disturbances of this function have not been implicated in the pathogenesis of hepatic coma Fatty changes in the liver sometimes occur in nutritional deficiency in the experimental animal this is considered by many to be a prelude to fibrosis (cirrhosis) (22) Such disturbance in fat metabolism leading to accumulations of fat in the hepatic cells may so impair liver function as to result in hepatic coma but the altered fat metabolism itself appears to bear no specific relation to the change in the state of consciousness In fact, there is no evidence that faulty or inadequate food intake is important in the genesis of hepatic coma in itself except that an insufficient caloric or a too high protein intake may lead to a disturbed ammonia metabolism

The liver is the only site of blood ketone formation, but as shown three decades ago it is decidedly not one of the sites of ketone removal No evidence of an upset in this metabolic process has been ascribed to patients with hepatic coma It may be mentioned in passing that diarrhea sometimes a distressing symptom in severe hepatic disease particularly hepatic coma may be induced or increased by giving large quantities of fat by mouth This observation has not been well documented but will bear further investigation

VITAMINS —Many of the vitamins especially those of the B complex function in metabolism as coenzymes Whether the liver has a specific role in rendering these vitamins suitable for use by the body tissues is not known It was noted above that the blood content of thiamine pyrophosphate (cocarboxylase) is somewhat deficient in severe liver disease Many of the other vitamins require phosphorylation to become active coenzymes There is no evidence that the liver is necessary for this process however Obviously patients with severe liver disease who have been on an inadequate diet may have dietary vitamin deficiencies It is doubtful however that these contribute to hepatic coma since most of the patients in whom hepatic coma develops are given large doses of vitamins both before and during the attack without either preventing the coma or improving the state of consciousness once impending coma or coma has set in Nevertheless occasional reports have indicated that massive doses of some of the vitamin B com

plex have produced improvement Little data is available on the role of disturbed vitamin metabolism in the genesis of hepatic coma, and much more work remains to be done

ENERGY METABOLISM —Direct measurements of energy metabolism in severe liver disease and particularly in hepatic coma, are virtually unknown However this should be a fruitful field for further investigation As noted above in hepatic coma the concentration of pyruvate in the blood is high particularly after glucose administration Seligson (39) found this to be true for a number of other organic acids as well including some from the citric acid cycle particularly alpha ketoglutaric acid and suggested this as presumptive evidence that the cycle was impaired As the oxidation of these substances generates high energy phosphate bonds their deficiency might be expected in severe liver disease and particularly in hepatic coma He further pointed out that many reactions of the liver including formation of urea from ammonia require high energy phosphate The exact manner in which the functioning of the citric acid cycle is impaired is unknown If energy production is in fact reduced because of a disturbance of the citric acid cycle further investigation may help to elucidate the production of hepatic coma

TREATMENT

No specific treatment for hepatic coma has been described although a few patients have appeared to respond to one or another of the therapeutic measures discussed below The equivocal phrase appeared to respond is used advisedly since spontaneous remissions largely temporary but in a few cases permanent are definite although infrequent occurrences The evaluation of specific therapeutic measures is therefore difficult and the use of the patient as his own control is hazardous Remissions are most common in coma precipitated or accelerated by one or more of the factors now known to be precipitants These factors—drugs infection surgical procedures and disturbances in water and electrolyte metabolism—merit discussion in some detail for avoidance of the precipitants may prevent or at least delay the onset of hepatic coma

PRECIPITATING FACTORS

DRUGS —The precise relation of central nervous system depressants to the genesis of hepatic coma has not been made clear Nevertheless

any of the hypnotic or sedative drugs will induce or at least accelerate the appearance of hepatic coma in susceptible individuals Unfortunately the noisy delirium and inappropriate behavior so often present before the onset of coma sometimes for days or weeks make administration of a hypnotic or sedative highly desirable All too often in such cases sedation and sleep merge gradually or rapidly into stupor and deep coma often irreversible and fatal The decision to use one of these drugs therefore calls for great caution There is no reliable method as yet, of determining the susceptibility of patients except that those with signs of impending hepatic coma are highly susceptible Otherwise the best criterion is severity of the liver disease weighed against the need for the drug Some drugs are less harmful than others and dose and frequency of administration become highly important considerations when sedation is necessary

Morphine even in small doses should rarely be given to patients with severe liver disease it has a prolonged action presumably because it is conjugated with glucuronic acid by the liver an activity greatly decreased in hepatic disease Methadone is probably in the same category it is also metabolized by the liver although no clinical studies have been reported In addition to its prolonged action morphine also has some antidiuretic activity which may add to the oliguria so often observed in these patients The use of N allylnormorphine in this condition has not been reported but presumably would be effective

Experiments indicate that removal of meperidine (Demerol) from the body is not as dependent upon the liver as that of morphine The former would therefore seem to be more suitable than morphine for the relief of pain in hepatic disease and clinical impressions support this Even meperidine however is not without danger for cases of hepatic coma have developed after its use

It is surprising how little is known of the risks of paraldehyde in the presence of severe hepatic disease in view of its frequent use in treating the neurologic complications of acute alcoholism and alcohol withdrawal Presumably this drug too is metabolized at least to some extent by the liver Clinically the characteristic paraldehyde odor can be detected on the breath sometimes for days after its administration to patients with liver disease Better laboratory evidence of its prolonged action is needed but enough is known to prohibit its use when severe liver disease is present, especially with signs of impending

hepatic coma except under unusual circumstances Without question many instances of hepatic coma have followed the administration of even a single dose of paraldehyde

On first thought the widespread use of barbiturates would make their implication in the pathogenesis of hepatic coma seem doubtful Nevertheless many of these compounds are detoxified by the liver particularly the thiobarbiturates such as Pentothal, and the long chain shorter acting compounds (8 36) The longer acting short chain barbiturates for example phenobarbital but particularly barbital itself are largely excreted by the kidneys There is reason to believe that they are less harmful despite which hepatic coma has occasionally occurred after repeated administration of phenobarbital even in small quantities (½ grain 3 times a day) Some doubt has been cast upon the presumed delay in excreting some of these compounds when liver disease is present (40) Nevertheless clinical evidence strongly suggests that all should be used with caution particularly those known to be metabolized by the liver

Little is known about the effect of anesthetic agents upon the liver or their possible action in inducing or accelerating the appearance of hepatic coma Certainly chloroform damages the liver and is rarely used under any circumstances and should never be given to patients with liver disease Many of the other inhalation anesthetic agents when given in large amounts over long periods of time are also harmful to the liver but to a much slighter extent Although the damage may not be of great consequence care should be exercised in using anesthesia in patients with evident liver disease There is no unanimity of opinion about which of the other anesthetic agents is least harmful to the liver Many believe that cyclopropane is a safer anesthetic than ether (5) Local or spinal anesthesia should be the method of choice when possible Little is known of the metabolism of procaine and its derivatives by the damaged liver

INFECTION —Sudden infection such as pneumonia meningitis or peritonitis in susceptible patients will precipitate hepatic coma While particularly true of patients already exhibiting signs of impending coma the same may be said of occasional individuals with severe liver disease who do not exhibit these signs Great care should be taken to avoid infections For example simply changing a patient s position in the bed or getting him out of bed for short periods of time even though he may be ill may prevent pneumonia Antibiotics should be given whenever necessary either for prevention or therapy De

hydration with resultant oliguria is possibly one of the most important complications of infection in hepatic disease and it may explain the effect of infection in these patients. The aim should be a normal urinary output when it can be achieved without overhydration

SURGICAL PROCEDURES.—Although surgeons well know that major operations are hazardous for patients with severe liver disease the reasons are little understood. Among the mechanisms may be included the possible damaging effect of anesthetics upon the liver the consequences of the use of hypnotics and analgesics the profound effects of surgical procedures upon water and electrolyte balance the results of tissue trauma and shock, especially upon ammonia metabolism and possibly many other factors Patients with severe liver disease should be given minimal doses of preanesthetic hypnotics and morphine should be avoided under any circumstance The choice of anesthetic agents is a difficult one other than avoiding chloroform Whatever the anesthetic used the goal to strive for is the shortest possible duration of the operation

Surgical procedures tend to induce sodium and water retention, especially if hypotension or shock occurs Body loss of potassium may also occur in the first few postoperative days These fluid and electrolyte disturbances may aggravate those found in chronic liver disease and in hepatic coma particularly the oliguria which may be increased nearly to anuria postoperatively High blood potassium concentrations may also occur and contribute to the condition

A major surgical procedure traumatizes tissues and results in release of intracellular substances and their degradation products—not only potassium but also breakdown products of nucleic acids with possible release of ammonia Presumably the substances thus released are neither properly metabolized nor excreted Shock may also raise the ammonia content of the blood to high levels it is assumed that the effect upon the liver of the severe alteration in circulation is the cause Experimental evidence to support these hypotheses is slight but it is known that a distinct rise in blood ammonia contents occurs in animals in shock (31)

Strict adherence to the general principles for handling patients with hepatic coma is essential when patients with severe liver disease undergo surgery particularly if there is evidence of impending coma In fact an operation is rarely advisable in the latter circumstance although occasionally it may be necessary and at times has met with success

The precautions to be observed with major operations are also necessary for minor procedures although to a lesser extent Abdominal paracentesis is particularly important in this respect Presumably it is not the procedure itself which is dangerous but the disturbance in fluid and electrolyte balance particularly the reduction in plasma volume oliguria and even peripheral vascular collapse which often follows paracentesis (21) Now that ascites formation can be controlled by a diet severely restricted in sodium paracentesis is seldom necessary (15 16) When it must be performed great care should be exercised in order to avoid complications It is noteworthy that repeated small paracenteses are better tolerated than a single large one In many patients it is true repeated paracenteses have had no ill effect but occasionally the procedure is followed by impending coma or deep coma and death

FLUID AND ELECTROLYTE BALANCE—The disturbed fluid and electrolyte balance in patients with severe liver disease and the possible increase in these disturbances from morphine administration acute infection surgical procedures abdominal paracentesis and the like make careful regulation of fluids and electrolytes mandatory This can be accomplished only by careful measurement of the total intake and output

In patients with impending coma it is usually necessary to catheterize or collect the urine in some other way to insure complete collection of the urine It is certainly required when deep coma is present The catheter should be irrigated at least once daily Despite the dangers of catheterization its use is not contraindicated in this circumstance Daily check of body weight often furnishes corroborative evidence An intake and output balance sheet which includes calculations for insensible loss and fluid contributed from the metabolism of food must be maintained These calculations are at best not completely accurate but they provide a far better basis for controlling the patient s hydration than would be possible otherwise

Supplementary blood and urine examinations especially the hematocrit level the serum sodium and potassium concentrations and the urinary sodium excretion will give additional evidence of the patient s status The blood nonprotein nitrogen and carbon dioxide contents should also be determined at frequent intervals When these facts and figures are available the patient s course can be evaluated from day to day If a surgical procedure especially paracentesis is contem

plated the determinations should be begun several days before so that the patient is well stabilized before he is subjected to the stress of surgery

Fluid balance —Briefly oliguria is commonly though not invariably present in induced or spontaneous hepatic coma In a patient whose previous fluid balance is not known it is always possible that the oliguria may be due to dehydration and a considerable increase in fluid intake may be attempted for 12 to 24 hours If diuresis does not result, the oliguria may be assumed to be caused principally by the severe liver disease and fluid intake must then be regulated by the output (including estimated insensible loss)

The blood hematocrit value is a means for following the patient s state of hydration along with fluid balance and body weight and similar measurements Frequent stool examinations for occult blood are desirable to detect gastrointestinal bleeding at the earliest possible stage Mild but persistent gastrointestinal bleeding usually not leading to severe anemia or profound changes in blood volume is a common complication of hepatic coma particularly in the terminal stages Occasionally the end stage of hepatic coma may be ushered in by massive gastrointestinal hemorrhage sometimes from varices but often only from multiple small areas of bleeding in the stomach and duodenum

Sodium —The serum sodium concentration is characteristically reduced in many patients with ascites Values of 130 or even 120 mEq per liter are common If the onset of hepatic coma leaves the hyponatremia unchanged treatment of the condition with hypertonic saline solution is unnecessary But if the serum sodium concentration declines progressively or if it is not known what the concentration was before coma developed hypertonic saline solution may be tried It may sometimes result in a dramatic improvement in the state of consciousness

Patients with marked oliguria are sometimes mistakenly given increased quantities of fluids orally or parenterally unless careful check of fluid balance has been maintained hemodilution and hyponatremia will result After gastrointestinal bleeding or if the blood volume is suddenly reduced by some other cause blood transfusions or intravenous administration of human serum albumin may reverse conditions and cause the patient to regain consciousness

Potassium —The serum potassium concentration is subject to marked

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SPECIFIC THERAPY

DIET—The importance of diet in the treatment of cirrhosis of the liver and viral hepatitis has been greatly emphasized by experimental work on animals and the classic studies of Patek *et al* (32) An adequate caloric, high protein, and vitamin intake is the basis of the commonly accepted treatment Fluid accumulations when present, are treated by severe sodium restriction It remains to be seen whether these same dietary measures should be used in hepatic coma Little is known about the caloric requirements of patients in coma but the assumption that barring fever restlessness or other forms of increased energy requirement the intake should be about 2,000 cal per day, *seems reasonable Much smaller intakes may require deamination of* protein to meet energy requirements with a concomitant release of ammonia Many patients may need a higher caloric intake because of the presence of one or more of the factors cited above

Despite the emphasis on a high protein diet patients with hepatic disease in most instances seem to do well with a normal protein intake such as that recommended by the Food and Nutrition Board of the National Research Council (1 Gm protein per kilogram body weight per day) A possible exception is viral hepatitis in which a shortening of convalescence has been reported following the use of a 19 per cent protein diet (10) In the presence of impending or actual hepatic coma the protein intake may have to be considerably reduced In fact, it is occasionally possible to induce hepatic coma simply by increasing the protein intake above the usual level As a rule most of our patients with impending coma have been given approximately 65 Gm of protein daily sometimes this is reduced to 50 Gm daily and occasionally when it is felt that the protein has contributed to the genesis of the condition a protein free diet is given for a few days

Feeding patients in actual or impending coma is usually a problem When possible frequent small feedings by mouth are best When this is impossible resort must be had to tube feeding a small plastic tube being most suitable† Homogenized milk to which cream may be *added to increase the caloric content is satisfactory for tube feeding* Sugar may be irritating to the bowel but many of the proprietary carbohydrate preparations containing polymers of hexoses are usually

† The plastic tubes of small bore furnished by Mead Johnson & Company have been found suitable for this purpose

variations in hepatic coma It is often normal but hypokalemia or hyperkalemia may be present, sometimes in the same patient at different stages Severe hypokalemia should be corrected occasionally correction of a severe hypokalemia may cause the patient to have a distinct turn for the better and regain consciousness Hyperkalemia is usually associated with oliguria or tissue destruction or both in such cases a rising nonprotein nitrogen concentration in the blood is usually evident The hyperkalemia is rarely severe enough to necessitate dialysis or other treatment

Nonprotein nitrogen —The nonprotein nitrogen concentration is usually normal or only slightly elevated in hepatic coma unless tissue breakdown or severe oliguria has occurred Rarely does the concentration rise to uremic levels and dialysis is seldom if ever indicated The blood urea concentration usually parallels that of the nonprotein nitrogen low blood ureas being seldom if ever found despite the fact that the liver alone is responsible for the manufacture of urea Presumably a decrease in urea formation sufficient to produce low blood urea concentrations would be incompatible with life because of the excessive amount of ammonia which would remain

Acid-Base Balance —The blood CO combining power or capacity in hepatic coma is usually normal or moderately reduced but the reduction is seldom sufficient or associated with a low blood pH to warrant therapy The reduction is assumed to be due to the presence of high concentrations of organic acids either from overproduction or from diminished excretion when oliguria is present or from both acting together

GASTROINTESTINAL HEMORRHAGE —Massive gastrointestinal bleeding usually from the upper part of the tract, is a common terminal event of chronic cirrhosis Varices a duodenal or gastric ulcer or gastritis may be the cause of the bleeding Whatever the cause frequent and repeated blood transfusions to replace blood loss and the use of inflated balloons in the cardia or lower esophagus have often been lifesaving procedures In many of the patients who recover hepatic coma develops within a day or two after the bleeding episode Presumably the shock from blood loss a complicating oliguria and the possible absorption of ammonia and other substances from the gastrointestinal tract combine to cause the coma Treatment of this type of coma requires particular care of fluid and electrolyte balance A few patients may recover but in general the prognosis is grave

dosage used this agent although theoretically plausible has little if any beneficial effect in the usual hepatic coma

Antibiotics —On the basis of older studies of Eck fistula in dogs and more recently of patients with cirrhosis it may be assumed that a good deal of the ammonia presented to the liver for conversion to urea comes from the colon and terminal ileum Dintzis and Hastings (13) found that gastrointestinal urease activity which presumably accounts for ammonia production, could be abolished by antibiotics Were ammonia the toxic substance causing hepatic coma antibiotic administration should be followed by a reduction of blood ammonia and clinical improvement Aureomycin and Terramycin by mouth and intravenously were tried several years ago by us and by others (17) The effect was inconstant and transient at best and appeared to induce gastrointestinal hemorrhage on several occasions Use of these or other antibiotics is not recommended until further study establishes their effectiveness

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well handled [‡] Oral fat occasionally induces or aggravates the diarrhea which is so often latent or present in moderate degree in these patients Parenteral administration of food should be resorted to only when oral or tube feeding is impossible or contraindicated Glucose or fructose with protein hydrolysates in suitable mixtures may be administered parenterally So far there is no evidence whether protein hydrolysates in the required amount are poorly tolerated in hepatic coma or will induce a high blood ammonia content further studies are necessary to establish this High concentrations of glucose from 15 to 25 or even 50 per cent may occasionally produce a satisfactory therapeutic response (23)

Although generally there is no evidence of specific vitamin deficiencies vitamins should be given routinely A multivitamin capsule may be given by mouth daily or a vitamin mixture may be added to the tube feeding formula [§] When deemed necessary multivitamin preparations may be given parenterally although massive doses are presumably not required

ADRENOCORTICAL STEROIDS —Some observers have noted a therapeutic response occasionally a dramatic one following the administration of large quantities of cortisone while others have reported a temporary improvement in the state of consciousness Ducci (14) gave 600 mg of cortisone per day to his patients with viral hepatitis and coma Less conclusive improvement has been observed after ACTH administration Use of these potent biologicals is not without risk, of course massive gastrointestinal hemorrhage has been observed following their administration to patients with chronic liver disease Evaluation of the effectiveness of these agents awaits accumulation of further data

GLUTAMIC ACID —Administration of the sodium salt of glutamic acid in hepatic coma in the hope that it would combine with the ammonia to form glutamine has met with only occasional success Suggestive decreases of the blood ammonia have occurred but favorable effects upon the state of consciousness have been reported only once (40a 40b 46) Impending coma following ammonium salt administration was not prevented by daily glutamate infusions (47) in fact in the

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‡ We have used Dextri-Maltose (Mead Johnson) and Dexin (Burroughs Wellcome)

§ We have used Vi Magna Multivitamins Granules furnished through the courtesy of Dr James Ruegsegger Lederle Laboratories Pearl River N Y

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The Pathophysiology of the Pancreas

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THIS REVIEW will deal essentially with the external pancreatic secretion and mainly with the inflammatory diseases of the pancreas The progress made in elucidating the pathogenesis of pancreatitis and in improving pancreatic diagnosis has resulted in considerable clarification of the mechanisms of its disease manifestations and in more rational and perhaps more efficacious therapy of its disease states

PANCREATIC PHYSIOLOGY

Our knowledge of pancreatic physiology has been derived from studies of *(1)* the mechanism of external pancreatic secretion and its control *(2)* the anatomy and physiology of the biliary and pancreatic duct systems *(3)* the protein metabolism of the pancreas and *(4)* the pancreatic response to stimulation in the presence of pressure disturbances in the pancreatic outflow tract

EXTERNAL PANCREATIC SECRETION

The pancreatic juice is an alkaline fluid composed primarily of a solution of bicarbonate which in man may reach a concentration of 140 mEq per liter The main function of the juice apparently is to adjust the duodenal contents to a pH suitable for the action of the pancreatic enzymes Trypsinogen is activated by trypsin and by the

on pancreatic function of a diet that is deficient in protein (148)

A possible interrelation with fat metabolism has been suggested by the occurrence of disturbed pancreatic function in patients with essential familial hyperlipemia, one of the inborn errors of lipid metabolism Furthermore hyperlipemia as such is not uncommon during the acute phase of acute pancreatitis (87)

Alcohol is believed to have a metabolic, if not a toxic effect on the pancreas (34 120) While the evidence for ethanol in this regard is rather weak, methyl alcohol appears to affect the pancreas through an intermediate metabolic pathway of protein synthesis Intense pancreatic necrosis is one of the lesions caused by methyl alcohol poisoning.

Pancreatic Stimulation and Disturbances of Pancreatic Outflow

The investigations of the early dissenters from the common channel theory are another source of experimental data on pancreatic pathophysiology Rich and Duff (129) initiated pancreatitis by forcible injection of sterile fluids other than bile into the duct of Wirsung Rupture of pancreatic ducts and extravasation of the fluids into the pancreas could be easily demonstrated Mann and Giordano (100) showed that the quantity of bile which had been used experimentally to produce pancreatitis by injection into the pancreatic duct was sufficient to rupture the ducts and flood the pancreas From these experiments it was concluded that it is not the bile itself which produces the pancreatitis but rather the pressure under which it is injected into the pancreatic tract

The foregoing should not invalidate the common channel theory completely but does emphasize that the significant pathogenetic factor in patients with anatomic common channels is the pancreatic duct obstruction rather than the biliary regurgitation While Rich and Duff's (129) ductal metaplasia hypothesis has not withstood the test of subsequent pathologic investigations other factors such as stone spasm of the sphincter of Vater vaterian stricture and edema have been reported to produce obstruction to the pancreatic outflow (4) Experimental pancreatitis may be induced by ligation of the pancreatic duct and stimulation of the pancreatic flow by secretin (97) Mecholyl or food by mouth (117) The resulting pancreatic secretion into a blocked tract leads to ductal rupture and pancreatitis

PANCREATIC OUTFLOW TRACT

Since Opie s (109) observation of the so called "common channel in 1901 the anatomic peculiarities of the terminal portion of the main pancreatic duct have been repeatedly stressed as a factor which in some instances could allow for the free mixing of pancreatic and biliary secretion Evidence of the existence of the common channel is the frequent finding of this configuration in postmortem studies and the cholangiographic visualization of the pancreatic duct in patients with pancreatitis (34) Its incidence has been variously reported as 20 per cent 76 per cent and 54 per cent (19 73 100) These figures nevertheless cannot be taken as absolute proof of the common channel hypothesis Biliary reflux is not assured by mere anatomic configuration especially since the secretory pressure relationships between the biliary tract and the pancreatic duct system would favor pancreatic reflux rather than biliary reflux (73) The secretory pressure of the pancreas is recorded to vary from 300 to 500 mm H_2O, that of the liver appears to be about 200 mm (136, 155) McGowan *et al* (105) noted that after morphine injection which produces sphincter spasm and thus a functional anatomic common channel pressures in the experimental animal well above that to be anticipated in the intact organism (above 500 mm H_2O) were necessary to force bile into the pancreatic duct system Pancreatic reflux is a common clinical observation in patients with choledochostomies on the other hand the presence of bile in the pancreatic tract is only rarely demonstrable in pathologic material (27) There has been an increasing tendency to question not only the frequency of biliary reflux but also its physiologic significance (72)

METABOLIC CONSIDERATIONS

In vitro study of surviving pancreas slices have pointed to the high rate of protein turnover involved in the synthesis of the pancreatic enzymes Recently profound morphologic and functional disruption of the normal animal pancreas has been induced by substituting the synthetic amino acid dl ethionine, in place of methionine (86) This drug produces the morphologic picture of acute pancreatitis including fat necrosis in time the acute inflammatory changes are replaced by *chronic fibrosis* and pancreatic acinar atrophy The pancreatic atrophy associated with kwashiorkor has also raised the problem of the effect

pancreatic hemorrhage and necrosis Popper *et al* (118) produced pancreatic edema by administering secretin after ligating the pancreatic duct necrosis followed when the pancreaticoduodenal artery was ligated in addition The vascular factor may be operative in arteriosclerosis in patients with arteritis and perhaps in essential hyperlipemia (90) Arterial and venous thrombosis can be readily demonstrated in histologic material in acute pancreatitis (143) Erosion of major blood vessels by pancreatic enzymes may cause hemorrhage into the bowel the retroperitoneal tissues or into the gland itself

Major pancreatic hemorrhage (pancreatic apoplexy) converts the gland into a boggy hematoma but most cases are not of this type Instead, varying degrees of edema necrosis and hemorrhage occur in different parts of the gland Collections of blood may burrow underneath the pancreatic capsule and along tissue planes retroperitoneally The necrotic pancreas may appear yellow black, gray or red depending on the degree and areas involved in the processes of infarction fat necrosis and hemorrhage Microscopically the cells are pale stain poorly and are in varying stages of disintegration in the most extensively damaged areas all structure is lost Surrounding the areas of necrosis and demarcating them from normal tissues is a zone of tissue debris and a layer of inflammatory cells Liquefaction of the detritus and collection of blocked pancreatic secretion gives rise to cystic structures within the zones of demarcation These structures may coalesce to become large sacs or cysts and perhaps are best called pseudocysts to differentiate them from the true pancreatic cysts which form within the duct system and are lined by endothelial cells rather than by inflammatory mesechymal cells (150)

As the pancreatic inflammatory process progresses edema and necrosis may burrow along the tissue spaces into the gastrohepatic ligament and retroperitoneally into the lesser sac In this manner necrosis and hemorrhagic areas may extend to the left subphrenic recess to the renal capsule and along the aorta into the pelvis Pleural effusions in the left side of the chest are reactions to inflammation developing under the left leaf of the diaphragm (11)

Fibrosis and calcification accompany resolution The edema and other inflammatory changes subside during the first week and areas of necrosis are autolyzed and replaced by fibrous tissue proliferation of parenchymal cells attempts to reduplicate the acinar and ductal morphology (8) By the end of a fortnight there may be such com-

PATHOGENESIS OF PANCREATITIS

Chronic pancreatitis is assumed to be the sequel of repeated or recurring episodes of acute pancreatitis The pathologic features of edema necrosis hemorrhage suppuration resorption and fibrosis are well documented from surgical postmortem and experimental studies These studies have led to the leading current concept that acute pancreatitis is a local autolytic disease process and that the common factor in all cases is the release into the pancreatic interstitial tissues of its activated proteolytic and lipolytic enzymes The process therefore is conceived as one of localized autodigestion and tissue disruption The latter is ascribed to the effects of the proteolytic enzyme action the fat necrosis to the lipolytic enzymes with secondary calcium precipitation

The ductal and/or acinar tissue must rupture with secondary extravasation of the activated enzymes into the interstitial tissues of the gland *before autodigestion can occur The important point is that* the proteolytic enzymes must be activated Enterokinase is the usual catalyst of trypsinogen but bile (not necessarily infected bile) can activate this enzyme Another set of factors has been receiving serious *scrutiny Trypsinogen and a trypsin inhibitor are apparently in equi*librium in pancreatic juice, a change in their ratio could lead to activation Kaiser and Grossman (86) studying ethionine induced experimental pancreatitis found that an increase in activated trypsin both in the pancreatic juice and in the gland substance occurs in association with a fall in trypsin inhibitor Such a shift has also been observed in direct studies of the pancreatic juice obtained by ductal cannulation in man

The initial pancreatic response to injury is edema and vascular engorgement (69) Gradually as autodigestion progresses the edema and exudation increase with distention of the pancreatic capsule and irritation of the posterior peritoneum Edema of the parenchyma may further obstruct the pancreatic duct system or block the tract if it has not been previously blocked Swelling of the pancreas within its capsule at first enhances pancreatic vascular engorgement but as the enlargement continues a vascular ischemia may be superimposed The ischemia may be the result of reflex vasospasm due to inflammatory irritation of the celiac ganglions The vascular factor in acute pancreatitis is extremely important As elsewhere in the body ischemia superimposed upon an inflammatory process results in infarction i e

pancreatitis has been the subject of some debate The proponents of the common channel theory have argued that infected biliary regurgitation is the responsible agent Others have suggested that chronic biliary disease affects the pancreas by reflexly inducing pancreatic duct spasm Direct spread of infection from the gallbladder to the pancreas is unlikely Such a pathway has not been demonstrable in anatomic dissections (91)

The association of alcoholism and pancreatitis has been extensively documented by observers who noted the high incidence of acute alcoholism preceding attacks of acute pancreatitis as well as a striking frequency of chronic alcoholism in patients with chronic pancreatitis (26) The high incidence of increased blood amylase values in patients treated for alcoholic gastritis and for delirium tremens has been noted in several reports (20) It has become increasingly apparent that alcoholics suffer from repeated mild attacks of pancreatic edema the cumulative effect of which is chronic pancreatitis The mechanism by which alcohol produces pancreatic edema has not been established It has been shown that unlike methyl alcohol ethyl alcohol is not a direct pancreatic poison nor can alcohol directly stimulate pancreatic secretion (16) Egdahl (55) has suggested that alcohol produces pancreatitis by initiating a gastroenteritis which leads to infection of the pancreatic ducts Proponents of the hypersecretion–obstruction theory of pancreatitis view alcoholic pancreatic edema as resulting from hypersecretion combined with pancreatic duct obstruction The latter is thought to be due to duodenal and papillary edema repeatedly demonstrated in postmortem material and to sphincter spasm initiated by the entrance into the duodenum of the large quantities of acid produced in the stomach under the stimulation of alcohol ingestion (18) The duodenal hyperacidity, upon impact with the duodenal mucosa causes the elaboration of large amounts of endogenous secretin (16) Thus alcohol may indirectly stimulate pancreatic flow (16) These dynamics may be further intensified by the ingestion of a large meal This hypothesis which explains the pancreatitis following alcoholic debauches and gourmandizing is analogous to the experimental pancreatitis produced by injection of secretin or mecholyl after pancreatic duct ligation

Finally pancreatitis may result after physical trauma (138) and following surgical procedures (51) such as gastrectomy (151) and splenectomy (5) in which the main or accessory pancreatic ducts are

plete histologic recovery that the pancreas appears completely normal In severe pancreatitis however resolution is delayed and residual fibrosis and acinar disruption persist (124)

The pathology of chronic pancreatitis is the end result of recurrent acute attacks (29) The parenchyma of the gland subjected to cycles of necrosis fibrosis and calcification is gradually replaced by fibrotic tissue (53) The cirrhotic process also involves the islet tissue Islet deficiency occurs relatively late since the pathologic process is always more severe in the region of the head thus tending to spare the body and tail of the pancreas where the islet tissue is concentrated Calcium *is deposited in the obstructed ducts and in the areas of fat necrosis* whenever the concentration of this ion rises above a presumed local critical level Areas of calcification thus form throughout the gland and within the ducts

ETIOLOGY

Based upon the pathogenetic concept outlined above and upon the *considerable experimental data dealing with the effects of pancreatic* stimulation in the presence of ductal obstruction it is currently believed that pancreatitis is the result of active pancreatic secretion in the face of an obstructed pancreatic outflow tract with consequent extravasation of activated enzymes into the tissue spaces of the gland While this represents an acceptable hypothesis it has not been definitely demonstrated so that it seems advisable to consider the multiplicity of possible factors involved in pancreatitis

The clear cut viral pancreatitis occurring during the course of epidemic parotitis is definitely of infectious origin (156) and pancreatic lesions are found in Coxsackie virus infections of suckling mice (111) Nevertheless infection accounts for only a small percentage of the cases of acute pancreatitis (38)

The association of chronic gallbladder disease and acute pancreatitis and the frequently beneficial effect that eradication of biliary tract *disease has upon coexisting pancreatitis remain* to be clearly explained (9) Over 70 per cent of the reported cases of acute pancreatitis have been associated with biliary tract disease and 50 per cent of the patients have cholelithiasis Gallstones in fact are six times more common in patients with pancreatitis than in the general population (2)

The manner in which biliary tract disease predisposes to or incites

not be demonstrated directly is reflected by a rise in antitryptic sub stances in the blood (78)

Disturbances in the electrolyte balance may also be encountered in the acute phase of pancreatitis Markedly lowered levels of sodium potassium and calcium in the serum have been reported (54) The changes in calcium have been especially stressed by Edmondson and Berne (52) This decrease in calcium which occasionally is great enough to produce tetany probably results from fixation of calcium in the areas of fat necrosis (52)

The occasional transient lipemia in the absence of errors of lipid metabolism is not clearly understood Perhaps it represents a shift to the phase of particulate fat absorption in terms of Frazer s partition hypothesis

Worth stressing is the fact that the endocrine function of the pan creas may be disturbed transiently or permanently as the result of acute and repeated episodes of inflammation involving islet tissue (89) The impaired carbohydrate tolerance with glycosuria and hyperglycemia probably represents a "true" pancreatic diabetes but the relative roles of the insulin producing beta cells and of the alpha cells presumed to secrete glucagon are not fully established

Two of the manifestations of chronic pancreatitis are noteworthy the severe pain and the symptoms of external pancreatic insufficiency It is far from clear why the fibrotic calcified gland with diminished secretion should be the seat of severe disabling pain When sufficient destruction of the pancreas has occurred so that most of the acinar tissue is replaced the defect in enzyme secretion and the resulting disorganization of fat and protein digestion will manifest itself as steatorrhea and azotorrhea (33) However fatty stools must be re garded as a relatively late sign of pancreatitis and even then need appear only when the digestion is overburdened by a high fat intake

DIAGNOSTIC AND PANCREATIC FUNCTION TESTS

Roentgenographic Features

Pancreatic roentgenography is difficult because the pancreas is a soft tissue structure which cannot be delineated from other structures within the abdomen There is no known method of visualizing the pancreatic ductal system other than by reflux from the common duct during operative or postoperative cholangiography Direct catheteriza

injured with consequent release of pancreatic ferments into the tissues in and about the pancreas When the pancreatitis of methyl alcohol poisoning, of hyperlipemia of kwashiorkor and the experimental ethionine induced pancreatitis are added it becomes apparent that multiple agents are involved in the pathogenesis Although the mechanism of active secretion against ductal obstruction may represent several large groups of the disease there is increasing evidence that mechanical factors cannot account for all cases of pancreatitis

MECHANISM OF DISEASE MANIFESTATIONS

Recent physiologic analysis has helped to elucidate the mechanisms by which pancreatic disease manifests itself The outstanding symptoms of pancreatitis are shock and pain Experimental studies of pain patterns produced by electric stimulation of various parts of the pancreas have indicated that pain arising in the pancreatic head tends to localize in the epigastrium to the right of the midline pain originating in the body of the pancreas tends to center in the midepigastrium and pain due to disease in the pancreatic tail is concentrated in the epigastrium to the left of the midline (13) Pain referred to the midback may occur with a lesion anywhere within the gland The pathways for pancreatic pain are the visceral afferent fibers which ascend via the sympathetic trunks It is noteworthy that balloon insufflation experiments have shown pancreatic pain to be frequently indistinguishable from pain evoked by distention of the gallbladder common duct or duodenum (24)

The release of activated enzymes into the interstitial tissues of the pancreas leads to localized swelling and edema This process may extend into the peritoneal cavity resulting in a localized peritonitis and fluid exudation Such a process gives rise to the localized ileus (recognized on roentgenograms as the sentinel loop" of jejunum) which is frequently seen in the disease

The systemic effects of acute pancreatitis presumably result from liberation of enzymes into the general circulation (142) Lipase and amylase enter the peripheral circulation the evidence for this is proved in animal experiments and is inferential in man Peripheral fat necrosis has been observed in the perinephritic fat and in the extremities Liberated trypsin is believed to account for the peripheral shock the cyanosis the hemorrhagic lesions and the alterations in the blood clotting mechanism (145) The hypertrypsinemia which can

able addition to the methods for evaluating the functional digestive capacity of the pancreas Decrease in blood calcium levels to values below 7 mg per 100 cc have usually been associated with a fatal outcome (52) Lowered potassium concentrations to levels below 4 mEq can be observed in about half the cases of acute pancreatitis (54) Hypokalemia is ascribed to lowered potassium intake loss by nasogastric suction excessive urinary excretion and to disturbed adrenocortical function which occurs with the associated alarm reaction The electrocardiographic abnormalities observed in acute pancreatitis by Gottesman *et al* (64) result in part from a decrease in blood potassium A marked leukocytosis is almost invariably present during the course of acute pancreatitis

Quantitative Tests of Pancreatic Function

The detection of evidence of functional abnormality of pancreas is limited by the fact that the organ has a large functional reserve and the capacity for rapid return to normal activity (46) The clinician in confirming pancreatic diagnoses therefore must depend on precise tests of pancreatic function In general the laboratory procedures can be classified as stool examination, determination of the pancreatic ferments in the blood investigation of coagulation properties of the blood and study of the duodenal contents

STOOL EXAMINATION —Disordered digestion in pancreatic disease manifests itself by diarrhea and/or steatorrhea with azotorrhea Simple diarrhea due to more rapid transit through the intestine may precede external pancreatic secretory deficiency The pathogenesis of this rapid transit time is obscure The fat, bulky, foul stools observed in patients with pancreatic disease are due to an insufficient secretion of enzymes for protein and especially fatty food digestion In some patients the enzyme deficiency is masked by the ingestion of a low fat diet Thus in order to obtain quantitative data in stool examination, the feces must be analyzed after the patient is prepared by a fixed high-fat diet for at least 3 days (33) The stool is examined for total nitrogen total fat fatty acid concentration and neutral fat

Stool analysis gives information not only on the completeness of digestion but also on the absorption of foodstuffs Incomplete enzymic digestion is reflected in a stool content high in nitrogen, total fat and neutral fat, and low in fatty acids On the other hand high nitrogen high total fat low neutral fat and high fatty acid contents

tion of the pancreatic duct has been practiced by Doubilet and Mulholland (35) to study the anatomy of the ductal system at the time of operation but as yet this cannot be accomplished as a preoperative diagnostic procedure Pancreatic lesions may be recognized by calcifications within the gland as in chronic calcareous pancreatitis within the ducts as in pancreatic stone or within cyst walls as in pseudocyst (115)

The roentgenographic signs of acute pancreatitis are the presence of haziness in the flat film obliteration of the psoas outlines elevation of the left diaphragm pleural effusion paralytic ileus and the so-called sentinel loop of jejunum in the left upper abdomen (63 66) If a barium meal can be tolerated elevation of the stomach and widening of the gastrocolic space may demonstrate the retroperitoneal enlargement of the pancreas (65)

Tumefactions and cysts are disclosed by their pressure effects on the surrounding viscera which can be visualized by barium (65) Cysts or pseudocysts of the pancreatic head by pressing on the second portion of the duodenum will result in enlargement of the duodenal curve and in extrinsic defects in the bowel outline and bulb shape (101) Mucosal distortion and luminal narrowing and displacement and fixation of the duodenal loop have been described Edematous enlargement of the papilla of Vater can often be demonstrated by careful pressure studies of the mucosa in the second portion of the duodenum The roentgenogram obtained under these circumstances may be indistinguishable from the reverse figure of three sign which Frostberg (59) has described as pathognomonic of papillary neoplasm

Laboratory Findings

The laboratory findings in pancreatitis are important not only in diagnosis but also as a gauge of the severity of the inflammatory process Glycosuria and hyperglycemia are seen in about 10 per cent of the cases of acute pancreatitis most frequently in the more severe cases In acute pancreatitis the disturbance of carbohydrate metabolism may be evanescent in chronic pancreatitis the diabetic state is more apt to be permanent (89) Althausen (2a) describes a starch tolerance test as a measure of the amylytic activity of the pancreas The test which compares the blood sugar curve after a test starch meal with the curve after glucose administration may prove to be a valu

is taken as an index of the severity of the pancreatitis slightly elevated levels interpreted as indicating mild pancreatic edema higher levels as indicating hemorrhagic and necrotic pancreatitis (116) This correlation of the severity of the inflammatory reaction with the degree of elevation of blood amylase has been challenged by many Small increases in amylase levels have been observed in mild clinical cases with rapid resolution as well as in patients with such extensive destruction of the pancreas that enzyme production was practically nil

Normally the serum amylase found in the blood is derived mainly from the pancreas and to a lesser extent from the salivary glands and the liver (74) The increased amounts which appear during pancreatitis have their origin in the pancreas the enzyme entering the blood stream in one of two ways by absorption from an obstructed duct into which the enzymes have been secreted, the back pressure hypothesis of Howard *et al* (74) or as a result of some alteration in the cellular permeability of the inflamed acinar cells which changes the partition ratio between the blood and the ductal system—the exocrine-endocrine theory of Janowitz and Hollander (83)

1 The validity of accepting minimal elevations of amylase levels as absolute proof of acute pancreatitis has recently been questioned (122) on the basis of reports of such increases in a variety of conditions such as perforated peptic ulcers acute and chronic biliary tract disease biliary dyskinesia (144) uremia after cholangiography (75) and after morphine or codeine administration (67) However they are not a common occurrence and scarcely detract from the usefulness of the amylase determinations High blood amylase levels are not seen in these conditions and can be accepted unequivocally as indicating pancreatic disease

2 The finding of normal blood amylase is never conclusive evidence of the absence of pancreatitis This disadvantage of the serum amylase determination has led to the use of the serum lipase value Serum lipase values parallel those of serum amylase but elevated lipase levels occur later in the course of pancreatitis and tend to persist longer than amylase increases When pancreatitis is a complication of epidemic parotitis the diagnosis can be confirmed only by serum lipase determination the values are increased in such cases The serum lipase thus complements and increases the usefulness of the serum amylase determination (28) Unfortunately many laboratories

indicate incomplete absorption Theoretically such a differentiation is sound in practice however the findings may be obscured by variations in bacterial digestion and in the intestinal transit time which affects both the completeness of digestion and the extent of absorption When the transit time is rapid, these factors may be so affected that pancreatic and nonpancreatic steatorrhea cannot be differentiated with certainty (47) Recently an attempt has been made to overcome this difficulty by oral feeding of an albumin tagged with radioactive iodine Fecal and urinary excretion of this tagged atom are measured for 72 hours thereafter The fecal excretion of I^{131} is reported to be higher in patients with pancreatic disorders than in patients with nonpancreatic digestive disturbances The abnormality of excretion noted was observed to be reduced in these instances by the administration of pancreatic extract (25)

It must be emphasized that changes in stool composition occur primarily in the advanced stages of pancreatic disease Even then the abnormalities may be masked by a low fat diet and evidenced only when pancreatic digestion is overloaded by a high fat intake (30) It is not so much that the pancreas has a tremendous reserve digestive capacity but rather that intestinal and peptic digestion are able to accomplish the degradation of simple carbohydrates and proteins This has become increasingly clear as surprisingly minimal digestive disturbances have occurred in some patients following total pancreatectomy (17 149) Moreover it has been demonstrated by studies of the pancreatic secretion that reserve digestive capacity cannot be equated with reserve secretory capacity (46) Analysis of the stool therefore cannot be used as a sensitive test of pancreatic function (47)

Blood enzyme determinations —The demonstration by Elman (56) that pancreatic duct occlusion and/or pancreatic inflammatory reactions result in an immediate but transient serum amylase increase remains one of the major contributions to the diagnosis of pancreatic disease Indeed determination of pancreatic enzyme levels is the most commonly employed laboratory diagnostic procedure in general use Serum amylase is the most easily measured enzyme Elevations of the serum amylase above the statistical normal range (which depends upon the method employed) occur within the first 72 hours of illness Small increases particularly in pancreatic edema, may be transient, so that early and frequent amylase determinations are imperative In some clinics the height of the serum amylase value

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duction (methacholine, bethanechol) and/or (3) blocking of the out flow tract of the pancreatic duct system (morphine, bethanechol) Depending upon the stimuli used, two types of response have been described—that in which the stimulus causes a rise in serum amylase in normal subjects (failure to rise is then indicative of pancreatic in sufficiency, as seen in pancreatitis) and that in which the stimulus does not cause elevation of the serum amylase in normal subjects but does induce an increase in patients with pancreatic duct obstruction (a positive response has been taken to indicate pancreatic cancer) (137)

Many studies have clearly indicated that pancreatic secretogogues and drugs with tonic effects on the sphincter singly or in combination can evoke small transient elevations in blood enzyme content Using some combinations of drugs differences in the averages can be shown between groups of patients with pancreatic disease and control groups but with a significant overlap of figures (48) This makes it impossible to establish statistical criteria for diagnosis With other combinations the alterations in blood amylase appear to occur in an unpredictable fashion in both groups of patients Some observers have concluded that the provocative blood enzyme tests show promise of diagnostic importance but the majority have expressed doubts of the diagnostic possibilities It seems likely that these procedures will be relegated to the status of a biologic phenomenon rather than that of a diagnostic test (48)

3 DETERMINATION OF BLOOD COAGULATION PROPERTIES —The clinical manifestations of a basic change in the blood coagulation mechanism which occurs in acute pancreatitis are well known Presumably this is due to hypertrypsinemia (80 145) but until recently there were only sporadic attempts to use this alteration as a diagnostic aid in pan creatic disease Innerfield and associates (77–82) deserve much credit for the interest in this field aroused by their extensive reports indicat ing a potential diagnostic significance of the plasma antithrombin titer in acute pancreatitis and in other abdominal diseases associated with abnormal pancreatic function Although the nature of this plasma antithrombin has not yet been defined these investigators suggest that the antithrombin level depends in part upon the rate at which the proteolytic enzymes are released from the pancreatic tissues into the blood stream

The same group (81) has reported elevated antithrombin titers in patients with acute pancreatitis even after the blood amylase has re

do not perform lipase determinations because the procedure is complicated the analysis time is long and the physical conditions of incubation are difficult to define (84)

Some investigators have attempted to diagnose acute pancreatitis in the later phases or in patients with normal values of blood amylase by studying the urinary amylase (31) Amylase is excreted by the kidney as a threshold substance When the blood amylase is high, there is a great increase in the urinary amylase unless there is concomitant renal insufficiency (37) The urinary amylase therefore tends to parallel the blood concentration except that extremely wide variations occur normally with changes in urinary specific gravity Hence urinary amylase concentrations have little practical value (47) when they are greatly elevated increases in the blood amylase can be demonstrated On the other hand the total urinary amylase in a 24 hour collection is of diagnostic significance because an increased rate of amylase excretion may persist after the blood amylase concentration has returned to normal This difference between urinary amylase concentration and rate of urinary amylase excretion is important but is often overlooked

The diffusion of pancreatic amylase and lipase may occur not only into the blood but also into the peritoneum A peritoneal tap in addition to revealing the classic beef broth fluid of acute pancreatitis may also be of diagnostic value by showing high amylase and lipase values Occasionally elevated amylase values may be found in sympathetic pleural effusions

While opinion is unanimous on the value of blood enzyme determinations in acute pancreatitis there is no such agreement about their worth in chronic pancreatitis (133) In the latter condition elevations of blood amylase levels are assumed to be the result of obstruction to the flow of pancreatic juice through a ductal system which may be compressed by fibrous tissue or occluded by calculi In practice, increased values are rarely seen and are usually correlated with exacerbations or recrudescence of acute inflammation

Attempts to overcome the deficiencies of blood enzyme determinations in the diagnosis of acute pancreatitis and to broaden their scope to include chronic pancreatitis have resulted in the provocative blood enzyme tests (48) In these the level of the enzymes in the blood is studied at intervals for several hours before and after the administration of drugs either singly or in combination which produce one or more of the following effects upon the pancreas (1) stimulation of the flow of pancreatic juice (secretin) (2) stimulation of enzyme pro

duction (methacholine, bethanechol) and/or (3) blocking of the out flow tract of the pancreatic duct system (morphine, bethanechol) Depending upon the stimuli used, two types of response have been described—that in which the stimulus causes a rise in serum amylase in normal subjects (failure to rise is then indicative of pancreatic insufficiency, as seen in pancreatitis) and that in which the stimulus does not cause elevation of the serum amylase in normal subjects but does induce an increase in patients with pancreatic duct obstruction (a positive response has been taken to indicate pancreatic cancer) (137)

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turned to normal High titers were also observed in pancreatic cysts (82), cancers (79) and sometimes in chronic pancreatitis Low titers were found in cystic fibrosis of the pancreas and in pancreatic cal cinosis (77) Although some experimental evidence seems to explain the clinical observations critical comparative studies of the plasma antithrombin levels in various inflammatory, degenerative and neo plastic diseases have furnished conflicting evidence In our laboratory the antithrombin titer has behaved much like the serum amylase value It is often elevated in patients with acute pancreatitis whose blood amylase is increased occasionally it is elevated in patients in whom the blood amylase has returned to normal levels In patients with chronic pancreatitis the antithrombin titer may be low normal or elevated The weakness of the antithrombin titer as a test procedure lies in abnormal values found in a significant percentage of control subjects (49)

Shingleton *et al* (141) have introduced the Paritol blood coagulation test for pancreatic disease In this test a change in the blood coagulability could be induced by the administration of a pancreatic secretogogue Prostigmin to patients with chronic relapsing pan creatitis and pancreatic cancer This alteration was not observed in normal subjects

EXAMINATION OF DUODENAL DRAINAGE —This permits direct study of the external pancreatic secretion, observation of the function and pat ency of the biliary tract and search for neoplastic cells The external pancreatic secretion is most reliably studied by the secretin test, a laboratory procedure derived from the investigations of Agren Lager lof and Berlund (1) These observers succeeded in producing a se cretin which was free of cholecystokinin activity and which could be injected intravenously

The secretin test is performed after the patient has fasted for 12 hours A double lumen gastroduodenal tube is positioned under fluoroscopic control at the ligament of Treitz In this position all the apertures of the longer division of the tube lie entirely in the du odenum and all the openings of the shorter division are confined with in the stomach By placing both outlets of the tube under constant suction uncontaminated gastric and duodenal juices can be obtained quantitatively The first specimens are discarded After a 20 minute control or basal period 1 clinical unit of secretin per kilogram of body weight is injected intravenously thereafter four samples of gastric

and duodenal juice are obtained at 20 minute intervals An 80 minute collection time is used because this is the interval required for the submaximal stimulus to the pancreas to be dissipated (39)

The following determinations are made on the samples obtained volume bicarbonate concentration amylase concentration, pH, guaiac reaction biliary pigment concentration and cellular morphology. The guaiac reaction may be of great assistance in pinpointing the source of bleeding in patients with guaiac-positive stools With the improved methods of collection cytologic study of duodenal drainage is attaining increasing significance (134) Positive smears have been reported in a high percentage of patients with pancreatic cancer (94 106) but the diagnostic value of a negative smear is not great. Changes in total volume bicarbonate concentration and amylase secretion characterize the pancreatic response to secretin

In the normal individual injection of secretin is followed by an increase in the rate of pancreatic flow from less than 1 ml per minute to 4 or more ml The rate of flow quickly reaches a maximum and subsides to basal rates by the end of 80 minutes Depending upon body size 100 to 300 ml is secreted in this time When a main pancreatic duct is obstructed or when the secretory tissue is destroyed by a pathologic process the total volume is reduced

The bicarbonate concentration of the duodenal drainage after secretin injection rises and falls more slowly than the volume of flow The maximum concentration is attained after 20 to 40 minutes it may rise as high as 130 mEq per liter in normal subjects but in parenchymal inflammatory disease of the pancreas the maximum concentration is much lower.

Secretin does not alter the actual rate of enzyme production The concentration of enzymes in pancreatic juice following secretin administration must therefore vary secondarily and inversely as the rate of flow For convenience and according to the concept of parallelism of enzyme secretion, only amylase content need be determined in the secretin test The significance of enzyme concentration, in itself, is not great, it is the total enzyme production that is significant in the secretin test. A decrease in total enzyme content may occur directly in parenchymal disease of the pancreas or secondarily as a concomitant of a marked reduction in volume of flow such as occurs in lesions causing pancreatic duct obstruction

The range of normal values in the secretin test can be derived from

a statistical study of the response of normal subjects The values will vary slightly depending on the type of secretin used length of collection period and other details of technic Since there is no evidence of the existence of hyperfunction of the external pancreatic secretion as a clinical entity in actual practice the lower limits of the ranges found are the critical values e g volume 2 ml or more per kilogram maximum bicarbonate concentration 90 mEq per liter total amylase secretion 6 units or more per kilogram By reducing the data on volume and amylase to a per kilogram basis statistical scatter is minimized (40)

The secretin test has little practical value in the diagnosis of acute pancreatitis (46) Patients who are seriously ill usually cannot be subjected to the procedure so that the diagnosis of acute pancreatitis must depend upon the clinical picture and the demonstration of an elevated blood amylase or lipase level or abnormal antithrombin titers The characteristic response to the secretin test in acute pancreatitis is a decrease in all three factors In actual practice any all or none (volume bicarbonate concentration and enzyme content) may be abnormal since the functional capacity of the gland paralleling its histologic behavior rapidly returns to normal within the first week of illness Thus a normal response to the secretin test does not exclude the diagnosis of acute pancreatitis The secretin test findings in acute pancreatitis have greater clinical significance in prognosis for persistence of abnormal findings after subsidence of clinical symptoms is indicative of permanent pancreatic damage and augurs the syndrome of chronic pancreatitis

Abnormal secretion is consistently encountered in chronic pancreatitis (46) The characteristic change revealed by the secretin test is a marked depression of the bicarbonate concentration to values between 25 and 50 mEq per liter The values for volume and enzyme concentration may be normal except in the advanced cases It has not been established whether this dissociation indicates a differentiation of function between the acinar and intralobular cells or a differential loss of function of the secreting cells (58 68) The prominence of the bicarbonate defect in chronic pancreatitis does not imply that the ability to produce a potent buffering juice is more consistently lost than the ability to secrete enzyme but is rather the result of using a specific bicarbonate stimulus secretin which has little or no effect on enzyme production This defect of bicarbonate secretion is an extremely valuable guide to the presence of chronic pancreatitis in patients

before surgery and before the diagnosis becomes obvious by the onset of diabetes, steatorrhea, and/or calcinosis

Pancreatic tumors cause changes in pancreatic secretion by obstructing the pancreatic duct (42) The extent of the change in results of the secretin test depends upon the site and degree of ductal obstruction The characteristic finding is diminution of the volume flow. The bicarbonate concentration and enzyme secretion are depressed only in patients with total ductal obstruction long standing obstruction or extensive destruction of the pancreatic parenchyma The most abnormal results are found in patients with diffuse pancreatic tumors and tumors of the head of the pancreas because these obstruct a major pancreatic duct The secretin test is most valuable in disclosing cancer of the body of the pancreas, In the early stages, these tumors are almost impossible to recognize by any other diagnostic procedure. They should be suspected in patients presenting the symptom complex of weight loss midback pain diarrhea and mild diabetes of recent origin Diabetes itself does not affect the external pancreatic secretion Tumors of the tail of the pancreas do not alter secretin test results because these lesions neither obstruct a pancreatic duct nor involve significant portions of the pancreatic parenchyma Tumors contiguous to the pancreas have no effect on the response to secretin

The biliary pigment response in the secretin test is a measure and graphic description of the flow of bile into the duodenum during the collection periods (32) It thus depends upon the choleretic activity of the hormone If function of the gallbladder is normal bile disappears from the duodenal drainage during the test In patients lacking gallbladder function because of cholecystic disease or cholecystectomy high concentrations of bile are present throughout the test period Complete absence of bile during the test points to biliary obstruction In incomplete biliary obstruction in the postcholecystectomy state the biliary pigment response is that characteristic of normal gallbladder function and is therefore abnormal in patients without a gallbladder (43)

The pancreatic and biliary pigment responses are useful in elucidating etiologic factors in various disease syndromes of the intestinal tract. Precise localization of the lesion is possible in patients with obstructive jaundice (39) If there is evidence of both pancreatic and biliary tract obstruction the lesion must lie in the head of the pancreas if pancreatic function is normal in the presence of biliary obstruction the lesion must lie in the extrahepatic biliary tract if both

pancreatic and biliary responses are normal in jaundiced patients hepatocellular pathology is suggested Hepatitis itself does not produce a change in the pancreatic response to secretin but does alter the biliary pigment response The secretin test cannot be used to differentiate hepatocellular jaundice from obstructive jaundice In the post cholecystectomy syndrome the test may reveal chronic pancreatitis and/or the presence of a ball valve common duct leading in some patients to surgery which might otherwise be unnecessarily delayed and obviating unnecessary exploration in others (41) Among the diarrheas, idiopathic steatorrheas, and inflammatory diseases of the intestines it is occasionally possible to detect unsuspected pancreatic insufficiencies due to fibrosis (46) Such instances have been reported in patients with sprue, regional ileitis diffuse jejunoileitis and chronic ulcerative colitis Presumably the pancreatic fibrosis in these patients disclosed *as well in postmortem material is related to a severe* prolonged nutritional deficiency A possible etiologic relationship to kwashiorkor is suggested

Pancreatic biopsy.—The final measure in diagnosis is exploration and biopsy Yet it must be admitted that manual palpation of the pancreas is notoriously misleading and even biopsy specimens may give erroneous information (93) Surface biopsies may reveal normal acinar tissue due to regeneration Deep tissue excisions although more likely to reveal true pathology are dangerous Complications such as hemorrhage external pancreatic fistula and even death have been reported A negative pancreatic biopsy does not completely exclude the possibility of a deeply placed pancreatic malignancy surrounded as it often is histologically by an area of pancreatic fibrosis (121)

TREATMENT

The aim of therapy in pancreatitis is to restore to normal so far as possible all the physiologic disturbances just described There is as yet insufficient evidence to justify the basic premise that energetic treatment of acute pancreatitis will prevent the chronic disease although that *is our therapeutic hope*

Acute Pancreatitis

The initial problem in the management of acute pancreatitis is whether to choose *conservative or operative treatment* Formerly most

exploratory operations were performed because a positive diagnosis could not be made otherwise When pancreatitis was encountered at laparotomy treatment included drainage of the lesser sac (112) or some type of diversion of the biliary tract in order to bypass an existing common channel (128) Although increased diagnostic accuracy has diminished errors in diagnosis the problem of medical versus surgical treatment still exists Some prefer laparotomy in cases of acute pancreatitis for it is then possible to eradicate whatever pathogenic factors are found such as biliary tract disease biliary reflux biliary obstruction and pancreatic obstruction (128) However review of large series of cases with direct comparison of the medical and surgical treatment of acute pancreatitis, reveals a much lower mortality and morbidity in the medically treated cases (98) In most clinics early surgery for acute pancreatitis is now resorted to less and less

Energetic medical treatment should be the rule whether the clinical picture is mild or severe for it is impossible to predict which cases will remain mild and which will progress to critical complication Therapy of the acute phase is directed toward *(1)* relief of pain *(2)* correction of systemic manifestations of shock and electrolyte disturbances *(3)* depression or inhibition of active pancreatic secretion and *(4)* control of possible infection

Morphine and other opiates may effectively relieve pancreatic pain but their well known production of smooth muscle spasm especially of the sphincter of Oddi may intensify the anatomic basis for the pancreatitis at the very time when the patient is being afforded temporary relief (136) Demerol has a much slighter spasmogenic effect and will afford analgesia without the possibility of a deleterious side reaction

Nitrites and atropine may help to relax spasm of the small intestinal musculature and of the sphincter However these drugs must be used with caution in patients in shock and in some instances suffering from myocardial insufficiency

Methantheline bromide (Banthine bromide) appears to be the drug of choice for the relief of pain (140) Its inhibitory effect on gastric motility and gastric acid secretion minimizes the quantity of hydrochloric acid entering the duodenum and thereby lessens the endogenous stimulus to pancreatic secretion (3) Spasm of the sphincter of Oddi is diminished by the decreased flow of acid into the duodenum and by the vagal depressing or anticholinergic action of the drug (104) Tetraethylammonium chloride and hexamethonium chloride

have been used with similar rationale but they are not as efficacious and side reactions are more pronounced

Nerve block (10) and epidural block (110) have been of value in treating patients with persistent, excruciating pain especially those with marked chemical peritonitis Paravertebral sympathetic block and splanchnic block relieve pain by interference with visceral afferent fibers in the sympathetic trunks and with splanchnic nerves supplying the pancreas (60) Sympathetic nerve block also lessens pain by depressing pancreatic secretion and by affecting the pancreatic blood vessels Fractional epidural block is less reliable than nerve block and should only be used as an adjuvant to all other measures

In addition to relief of pain, supportive therapy includes strict attention to fluid electrolyte and blood requirements Shock is always an outstanding symptom of pancreatitis (142) and its severity may be far out of proportion to all other signs and symptoms The extent to which the blood volume is decreased has been appreciated only in the past few years Blood volume studies in acute pancreatitis have revealed deficits as great or greater than those observed in patients with acute small bowel obstruction Animal experiments have shown that the correction of these deficits by albumin infusions has a startling beneficial effect on the mortality of induced acute pancreatitis The greater attention which is now paid to blood volume requirements may explain the significant decrease in initial mortality in the earlier phases of acute pancreatitis (88)

The presence of shock therefore calls for replacement by blood plasma albumin and solutions of electrolytes sufficient to maintain normal blood volume blood pressure and adequate renal function *Glucose must be administered cautiously for it may aggravate a diabetic state precipitated by the pancreatitis* Rarely when there is marked hyperglycemia small doses of insulin may be necessary

Hypocalcemia is fairly frequent when blood calcium levels are low the prognosis is poor Calcium gluconate solution may be given intravenously as needed Hypokalemia is combated by potassium orally or with caution intravenously Blood potassium studies and electrocardiograms should be made frequently to avoid potassium toxicity (54)

Measures to depress pancreatic secretion are of paramount importance Nasogastric suction removes hydrochloric acid from the stomach before it enters the duodenum thereby preventing formation of endogenous secretin The withholding of all food and fluid by

mouth further lessens both gastric and pancreatic secretion Banthine and atropine are also useful Any effective diminishing of the pancreatic secretion "splints" the inflamed pancreas and interferes with the pathogenic cycle which would produce further pancreatic and peripancreatic lesions

Demonstration that a potent carbonic anhydrase inhibitor (Diamox) will depress or completely inhibit pancreatic fluid and bicarbonate formation offers the possibility of depressing pancreatic secretion directly at the cellular level (50) This agent is now under investigation

Irradiation of the pancreas is another mechanism for diminishing pancreatic secretion (123) It has not been used extensively in pancreatitis but there are reports of clinical benefits in cases so treated (95) Improved deep radiotherapy with rotation technics and radio cobalt may make it possible to deliver an effective dose to the pancreas with minimal skin damage and radiation sickness

Recently treatment of the local lesions of acute pancreatitis has been attempted by the use of specific enzyme inhibitors Soybean trypsin inhibitor has been reported to lessen the shock symptoms in acute pancreatitis but its administration is not without danger (135) Popper and Necheles (119) noted no change in the necrotic process in acute experimental pancreatitis but did claim some beneficial effect from the use of lipase inhibitors Human albumin contains a potent antitrypsin which can inhibit intravascular trypsin when the albumin is administered in quantities necessary to restore the blood volume deficit in acute pancreatitis (88)

Antibiotics have helped greatly to decrease the delayed mortality and morbidity in acute pancreatitis (96) The use of chemotherapy and plasma expanders has reduced the mortality of acute pancreatitis from about 50 to 10 per cent Penicillin and the tetracyclines are the most efficacious agents against the usual intestinal organisms found in the peritonitis of pancreatitis The drugs are usually administered parenterally yet certain experimental studies have indicated that oral administration might be more effective since it would sterilize the source of infection as well as the diseased areas The use of penicillin and the tetracyclines may be responsible for the apparent decrease in the late sequelae of abscess and pancreatic fistula

Chronic Pancreatitis

The treatment of chronic pancreatitis is difficult far from standardized and often disappointing Medical therapy which leaves much to

be desired includes a high caloric, high protein low fat diet supplemented by vitamins Small frequent feedings are advocated to minimize pancreatic secretion Alcohol is interdicted because of its effect on pancreatic secretion and its action on the duodenal mucosa and sphincter Substitution therapy includes pancreatic extract in patients with marked steatorrhea Pancreatin sometimes strikingly reverses the symptoms of external pancreatic enzyme deficiency

Despite all forms of medical treatment some patients continue to have excruciating pain progressive weight loss and progressive mental and physical deterioration Addiction to morphine and alcohol is common among these patients Surgery is the final therapeutic attempt, and the many procedures that have been advocated are an index of the diversity of opinions about the pathogenesis of symptoms and of the indifferent success of such treatment

The first point of attack is the underlying biliary tract disease which may be present (128) Removal of a diseased gallbladder produces a remission in about a third of one series of cases (61) The initial operation is the logical time to explore the common duct and to determine whether stone or inflammation is causing obstruction at the papilla

Procedures for obstruction of the distal common duct are dictated by the site and type of obstruction Stones are removed and prolonged drainage of the common duct is instituted (22) For ductal stenosis choledochoduodenostomy or a Roux Y choledochojejunostomy is thought to be superior to T tube drainage since the former completely divert the biliary flow from the pancreatic tract and by pass lesions at the papilla (61) Roux Y anastomosis minimizes retrograde regurgitation of intestinal contents into the biliary tree and therefore may be accompanied by a lower incidence of cholangitis and cholangiolitis and resultant biliary cirrhosis than does direct ductal enteric union (14)

Functional and organic obstruction of the periampullar region may be relieved by operations on the sphincter of Oddi (36) The original endocholedochal procedure though feasible has been discarded because occasionally the sphincter fibers are not interrupted and because fatal hemorrhage may occur Transduodenal sphincterotomy has proved safer and more effective (62 85)

Neurosurgeons have devised procedures designed to relieve the debilitating pain of chronic pancreatitis and to diminish pancreatic secre

tion Among advocated measures are stripping of the choledochal nerves from the common duct (126) splanchnicectomy (99) and sympathectomy with and without splanchnic section (125) Section of the vagus nerve has been combined with some of the procedures men tioned because of its spasmolytic action on the sphincter muscle and its inhibitory effect on gastric and possibly on pancreatic secretion Although interference with the autonomic nerves may afford palliation of symptoms the experimental and clinical evidence suggests that it does not affect the progress of the disease (131)

Gastrointestinal diversion may be necessary because of mechanical obstruction of the duodenum resulting from extensive fibrosis or from actual encroachment by a large cyst in the head of the pancreas Cattell and Warren (23) advocate gastroenterostomy for the relief of such obstruction and combine it with vagus nerve section Rich man and Colp (130) noting the beneficial effect on chronic pancre atitis which followed subtotal gastrectomy for gastric ulcer intro duced this procedure as a definitive treatment for pancreatitis They also advise bilateral vagisection to supplement the effect of the gas trectomy and base their treatment on the theory that it provides a "splinting" of the pancreas by suppressing gastric acid secretion and diminishing endogenous secretin formation

The direct surgical attack on the diseased pancreas includes opera tions designed to treat the complications of the inflammatory process procedures attempting to eradicate etiologic factors which initiate the recrudescences of inflammation and measures removing the diseased tissue itself

Purulent collections within the pancreas the lesser sac and the left subphrenic space are treated by incision and drainage The threat of spreading peritonitis and pancreatic fistulization is minimized by the use of chemotherapy and drugs such as Banthine which depress pan creatic secretion Pancreatic cysts or pseudocysts require surgery only when because of size or location symptoms result from encroachment on adjacent viscera Extirpation the definitive treatment, is not al ways possible especially in lesions of the pancreatic head and if feasible is not always desirable because of the extensive surgery re quired for excision Evacuation and marsupialization on the skin have been discarded both because of recurrences and because of subse quent development of an external pancreatic fistula (114) Internal drainage by simple anastomosis of the cyst to the stomach (15) to the

duodenum or to the jejunum by what appears to be the procedure of choice—a Roux Y cystojejunostomy (132)—obviates the nuisance of external drainage and the loss of pancreatic juice and electrolytes These procedures return the pancreatic enzymes to the intestine The hazard of regurgitation of chyme into the cyst cavity is lessened by the Roux Y *anastomosis*

A number of procedures designed to overcome pancreatic duct ob struction have been suggested but have not had sufficient clinical trial to warrant conclusions on their value (152) Among these are pan creaticolithotomy (102) ligation of the main pancreatic duct so as to destroy completely the acinar tissue (127) and transection of the main pancreatic duct followed by immediate reanastomosis to the duodenum (21) Relief of pancreatic duct obstruction in a retrograde fashion has been attempted by implanting the tail of the pancreas or *the distal end of the pancreatic duct into a loop of upper jejunum* (157) Du Vals (51a) caudal decompression of the pancreas seems a sensible solution of the problem of obstruction in the duct system distal to the sphincter

Pancreatectomy is the final desperate step reserved for those in capacitated individuals in whom all other measures have failed Re sections of the left half of the pancreas in those rare cases in which the disease is limited and more severe in the tail presents no technical difficulty and the results are gratifying In the majority of patients however the disease process is more diffuse and most severe in the region of the head Distal pancreatectomy is of doubtful benefit in *such cases* (23) *and total pancreatectomy is required* (154) Total pancreatectomy implying as it does resection of the duodenum and a *choledochal anastomosis* is an *operation of such magnitude and high* mortality that many hesitate to advocate this procedure for a non malignant lesion The diabetes and metabolic disturbances which fol low pancreatectomy may substitute one type of invalidism for another in these unfortunate patients (57)

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Clinical Significance of Serum Mucoproteins*

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THE PRESENCE in human serum of a heat-stable protein complex soluble in strong acid protein precipitating agents has been known since 1892 (1) In normal man this complex represents about 1 per cent of the total serum proteins and 8 to 9 per cent of the total protein bound polysaccharide This strikingly high proportion of bound carbohydrate is associated with an acidity exceeding that of all other known serum protein fractions Recent interest in this chemically unique protein complex has been stimulated by the biochemical studies of Winzler and associates (2–5) who named it "serum mucoprotein" The older biochemical literature is replete with descriptions of serum components with mucoprotein like characteristics This has resulted in a multiplicity of confusing terms usually based on differences in the sources isolation technics and methods of measurement of these carbohydrate rich proteins Among the diverse terms are seromucoid (6 7) index of polypeptidemia (8) polarographic filtrate wave (9) blood proteose (10) seroglycoid (11) globoglycoid (11) serum glycoprotein (12) acid glycoprotein (13) orosomucoid (14) acid protein (15) alpha$_1$ glycoprotein (16) mucopolysaccharide (16) and fraction VI mucoprotein (14) The data relating to these various proteins cannot be strictly compared unless attention is directed to the precise differences in the chemical characteristics of the serum components measured

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bound carbohydrate of normal human serum The serum mucoprotein derives taxonomic significance as a discrete easily isolated well defined serum glycoprotein which is labile and responsive to many pathologic changes and can be quantitatively measured by routine clinical methods The term "mucopolysaccharide" although employed in the past to describe mucoprotein like substances should be reserved for nonprotein containing mucoids such as chondroitin sulfuric acid compounds Their occurrence in the serum in any measurable quantities has not been established

The electrophoretic mobility (4, 5) of both normal and pathologic mucoprotein is identical with that of the α_1 globulin In the normal subject, mucoprotein comprises about one fourth of the total α_1 globulin fraction Marked increase of the mucoprotein level is often but not always accompanied by parallel changes in other α globulins In some pathologic conditions the mucoprotein (M) level may rise independently and in others fall inversely compared to other α globulin constituents Thus the M level represents a variable proportion of the total alpha globulins and of the total serum glycoprotein Mucoprotein, which normally accounts for 1 per cent of the total protein and 8 to 9 per cent of the total protein bound polysaccharide may in some common inflammatory or neoplastic diseases (17) contribute as much as 5 per cent of the total serum protein and 20 per cent of the total bound polysaccharide of the serum The approximate quantitative relation of mucoprotein to other glycoprotein components and to the major globulin fractions can be simply determined by a battery of indices (18) These include in addition to the mucoprotein level the total serum polysaccharide (19) normally concentrated in the α_1 and α_2 globulins (Fig 1) the acid precipitable globulin (APG) turbidity (20) a guide to the status of α_2 plus β globulins and Kunkel s zinc sulfate (ZS) turbidity a measure of gamma globulin concentrations (21) Figure 1 shows graphically the relation of serum mucoprotein to the total serum polysaccharide and to the other globulin indices just mentioned

DETERMINATION OF SERUM MUCOPROTEIN CONCENTRATION

When whole serum is treated with such commonly employed protein precipitating agents as sulfosalicylic trichloracetic and perchloric acids all of the serum proteins except mucoprotein are precipitated

Serum mucoprotein should be classified as a glycoprotein (Fig 1) since it contains from 15 to 20 per cent carbohydrate linkages of the glucosamine and galactose-mannose polysaccharide types Other serum protein fractions containing 5 per cent or more of carbohydrate (16) have also been termed glycoproteins (Fig 1) The relative position

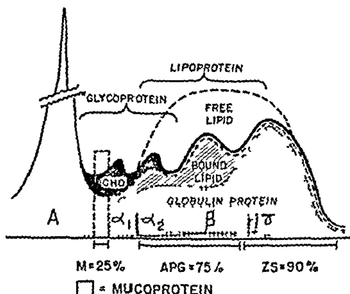


FIG 1—Relations of serum mucoprotein to other globulin fractions projected graphically against a boundary electrophoresis pattern The distribution of bound carbohydrate (polysaccharide and hexosamine) is shown by the black area confined mostly to the alpha globulin glycoproteins but also extending across as a thin line among beta and gamma globulin fractions Mucoprotein is superimposed as a discrete fraction (close stippled area) comprising about one-fourth of the alpha globulin fraction in normal serum APG turbidity represents about 75% of alpha plus beta globulin and ZS turbidity approximately 90% of gamma globulin measured electrophoretically For further details see text

of mucoprotein in the total serum protein spectrum may best be recognized by noting that all of the major globulin fractions contain varying amounts of bound carbohydrate whereas albumin is devoid of carbohydrate The beta and gamma globulins contain about 1 per cent carbohydrate compared to the alpha globulins with an average carbohydrate content of 5 per cent Since beta and gamma globulins normally contain proportionately small amounts of bound carbohydrate the term "serum glycoprotein" should be reserved for the alpha globulin proteins in which is concentrated about half of the total protein

Distinct physiologic significance may be attributed to the sex difference in the serum mucoprotein level in view of the known hepatic and endocrine factors which are involved in the maintenance of the levels in health and disease (24 27 28) In Winzlers (3) study of 18 normal men and women the mean level expressed as tyrosine was 3 0 mg per 100 cc and as polysaccharide 11 2 mg

PATHOPHYSIOLOGIC ASPECTS

The physiologic function of serum mucoprotein remains obscure despite the recent accumulation of much clinical and experimental data on diverse empiric factors which induce wide fluctuation in serum mucoprotein concentrations Winzler and Burk (10) first observed that the generalized increase in concentration which occurs in animals bearing transplantable tumors was also accompanied by distinctly higher levels in the veins leading from the tumors than in the venous heart blood Similar increases in serum content were noted in efferent veins from sterile turpentine abscesses The increase in mucoprotein formation resulting from such lesions was so great as to suggest that it could not be derived from tumor nitrogen even though it was apparently formed or liberated at the sites of increased proliferative activity of tissues They postulated that mucoprotein was formed by the degradation of serum albumin Subsequent studies indicated that this was unlikely since albumin lacks the carbohydrate moiety essential to the formation of mucoprotein By means of simultaneous serum and tissue studies with direct carbohydrate staining technic Catchpole (30) has recently found that an increase in mucoprotein like material occurred in the normal connective tissue abutting on transplantable tumors traumatized tissues and edematous pulmonary lesions He concluded that serum mucoprotein may be derived from the ground substance of the connective tissue resulting from the action of depolymerizing enzymes around the sites of invasive growth or increased proliferative activity of tissue

In their original study Winzler and Burk mentioned that the high serum mucoprotein levels usually found in normal tumor bearing animals failed to develop in animals with hepatic injury This observation was not amplified until recently when clinical and experimental data were obtained indicating that the local biochemical processes which occur at the sites of tumors and other pathologic lesions are mediated or regulated in large part by general metabolic factors in the host

(22) *Mucoprotein in the filtrate may then be precipitated by the* formation of an insoluble metal complex with phosphotungstic acid This simple differential precipitation procedure (23) can be used for routine use by clinical laboratories The concentration of mucoprotein may be measured in terms of its protein or its carbohydrate moieties Since the former comprises from 75 to 85 per cent of the total mucoprotein by weight such simple protein reagents as the biuret reagent (measuring peptide linkages) or the Folin reagent (condensing with *tyrosine groups) may be employed (22 23) to quantify serum muco*protein concentrations Measurement of the smaller carbohydrate moiety is not required for routine clinical determinations Because of its relatively unique chemical characteristics the separation and estimation of serum mucoprotein is quantitatively reproducible with an accuracy of 2 to 3 per cent and with an ease comparable to a blood sugar or a urea nitrogen determination

*Mucoproteins like other α–globulin fractions are relatively labile in vitro The apparent mucoprotein level of serum may be readily in*fluenced by changes in enzymic and coprecipitation factors which are easily induced by improper handling of blood or serum Thus the separation of serum within 1 to 2 hours after clot formation is necessary to obtain reproducible results Increasing concentrations are recorded when serum is improperly refrigerated or when blood is permitted to remain too long at room temperature before centrifugation Details of the several methods for performing mucoprotein determinations have been described elsewhere (2 22 23) Our experience has been most satisfactory with the biuret peptide method for estimating mucoprotein levels The concentration in plasma may be as much *as 30 per cent less than in serum and varies with the anticoagulant* employed (24)

NORMAL MUCOPROTEIN LEVELS

Levels are significantly higher in normal men than in women between the ages of 20 and 50 (25) Thus among 185 normal adults we found a mean level of 52 9 mg per 100 cc (expressed as biuret peptide) in women and a mean level of 59 2 mg in men A somewhat greater divergence *of values in normal men and women was reported* by Mandel (26) particularly between ages 15 and 25 above age 60 the sex differences appeared to dwindle In our studies of several thousand individuals a normal range of 40 to 70 mg per *100 cc for* women and 48 to 75 mg for men was used as a standard (27)

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particularly those involving hepatic and endocrine function Whereas in both man and animals tissue proliferative changes due to inflammation neoplasms trauma, surgery and radiation were found empirically to raise the serum mucoprotein level a functional failure of liver (25) pituitary (27), or adrenal glands (27 28) resulted in a lowering of the serum level (Fig 2) A possible renal excretory factor (27 31) has not yet been adequately explored

The importance of steroid metabolism probably mediated through the liver is suggested by the considerable sex difference (25) in mucoprotein levels of normal young adults The lower levels in women ap

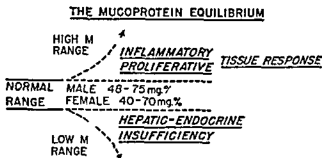


Fig 2—Pathophysiologic factors which may exert bidirectional influence on serum mucoprotein level

pears to be related to the low levels in patients with portal cirrhosis—this possibly representing an expression of altered metabolism of estrogens in the presence of parenchymatous liver disease The subnormal levels associated with portal cirrhosis (25) are probably not a consequence of a simple coprecipitation or a binding of relatively acid mucoprotein with the increased amounts of basic serum gamma globulins which usually occur in chronic liver disease Such an explanation would not apply to the low mucoprotein levels found in acute toxic hepatitis or in hepatitis without gammaglobulinemia nor *would it apply to panhypopituitarism or adrenal insufficiency* in which no hypergammaglobulinemia exists

A direct endocrine effect on the serum mucoproteins with the induction of rising levels results from ACTH administration (32 33) Reduction in levels follows experimental hypophysectomy and adrenalectomy (28) Roberts (34) noted that adrenalectomized tumor bearing animals had a lower level of the mucoprotein like alpha globulins than did nonadrenalectomized animals Animals given cortisone

showed an accentuated release of alpha globulins as compared to controls These observations provide a basis for including the serum mucoprotein among a number of "acute phase" reactants (35 36) i e, serum components which respond to the stressful or acute phases of rheumatic fever and other illnesses. Since rheumatic diseases are usually associated with high mucoprotein levels in the serum and an intact adrenal (and liver) seems to facilitate this response the designation of an "acute phase" reactant would seem warranted The response in mucoprotein levels may begin to appear within a few hours after a stressful event Thus the level begins to rise 4 to 8 hours after surgical procedures (24) and usually reaches a maximum in 3 days (Fig 3) The over all postoperative trend varies with the nature and extent of the surgical procedures the postoperative course and the preoperative level of mucoprotein If the broad generalizations of Selye regarding stress" in chronic disease were to be adopted the high serum mucoprotein levels in chronic infection collagen disease and advanced neoplasia might be considered as evidence of a chronic and adequate hyperadrenal response

Several studies with isolated mucoproteins suggest but provide little conclusive evidence that the serum mucoprotein concentration may exert an influence on blood coagulation or hemagglutination phenomena These investigations have been based on in vitro experiments with mucoproteins isolated from serum plasma or urine by procedures which involve some degree of protein denaturation Burnet (40) Tamm and Horsfall (37 38) and Stulberg *et al* (39) found that both human blood and urinary mucoproteins act as potent inhibitors of the virus hemagglutination reaction In these experiments mucoprotein competed with influenza mumps or Newcastle disease virus for adsorption onto the surface receptors of the erythrocytes According to Burnet the first step in the process of cellular infection by viruses is one of enzymic interaction with mucoproteins at the red cell surfaces What role if any the serum mucoprotein level might play in this interaction has not been determined Of possible significance is the fact that the blood group substances involved in hemagglutination phenomena are mucopolysaccharides (hexosamine and hexose) in vivo i e before chemical procedures involved in their isolation these substances probably contain a protein moiety

The acidic properties and high polysaccharide content of the serum mucoprotein fraction suggested its possible role in blood coagulation mechanisms (41) These characteristics are common to heparin and to

synthetic sulfonated polysaccharide esters with anticoagulant activity (42) A relatively weak antithrombin and antithromboplastin (heparinoid) action on blood clotting mechanisms in vitro was observed with mucoprotein and to a lesser extent with certain other carbohydrate rich globulin fractions isolated by phosphotungstic acid precipitation On a gravimetric basis the potency of 100 to 150 mg of mucoprotein so isolated equaled that of 1 mg of heparin It should be noted that this mucoprotein may be an artefact produced by the formation of a heavy metal-acid protein complex Nevertheless it might be somewhat significant that a heparinoid complex can be so easily formed from certain serum proteins in a fashion apparently analogous to the sulfonation of long chain polysaccharide esters The carbohydrate-protein linkage appeared to be essential to this phenomenon since noncarbohydrate containing proteins such as serum albumin pepsin and protamine did not manifest heparinoid properties after precipitation with phosphotungstic acid Isolated mucoprotein gave the metachromatic reaction with toluidine blue and combined stoichiometrically with protamine in vitro with blockage of the anticoagulant effect Although all pathologic serums with high protamine titration figures (43) also showed increased serum mucoprotein concentrations a positive correlation between mucoprotein levels and protamine titration was not always observed It was postulated that for mucoprotein to exert a clinically recognizable role as a circulating anticoagulant a sudden increase of 150 to 200 mg per 100 cc in the serum level would have to occur without counterbalancing or concomitant changes in any of the known more potent coagulation factors This combination of changes probably occurs so rarely that clinical evidence of a significant action of mucoprotein in coagulation disorders has not yet been obtained Nevertheless high levels of mucoprotein and other α-globulins rich in polysaccharides develop in certain hemorrhagic disorders these have not been fully explained on the basis of the older well defined coagulation factors Among such hemorrhagic disorders may be included obstetric shock (44) acute pancreatic disease (45) and certain types of advanced neoplastic diseases (46) Possibly the favorable effects of adrenal hormones in certain types of secondary atypical hemolytic anemias or in autoagglutinative disorders may be mediated through an influence on serum mucoprotein or closely related serum components This possibility remains to be explored

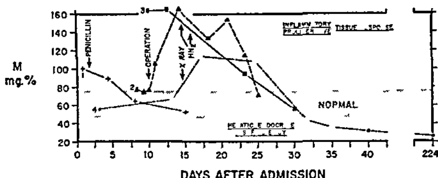


FIG 3 —Fluctuation in mucoprotein level as result of inflammatory proliferative, and traumatic tissue changes 1 penicillin treatment of lobar pneumonia 2 major abdominal operation (cholecystectomy) 3 nitrogen mustard treatment of generalized Hodgkin s disease 4 roentgen therapy of mediastinal Hodgkin s disease in patient with portal cirrhosis

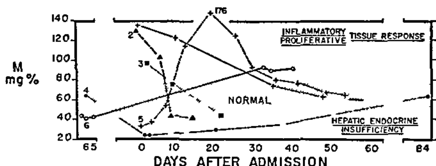


FIG 4 —Serial M patterns in patients with various types of hepatocellular disease complicated by coincident extrahepatic disorders 1 subacute bacterial endocarditis with hepatosplenomegaly responding to antibiotic therapy 2 acute epididymo-orchitis responding to antibiotic therapy in patient with portal cirrhosis 3 pneumonitis apparently responsive to antibiotics in patient with portal cirrhosis 4 homologous serum hepatitis after fulguration of a bladder neoplasm in patient suspected of carcinomatosis on hospitalization 5 acute carbon tetrachloride (inhalational) poisoning with recovery (see text for details) 6 portal cirrhosis with development of malignant hepatoma

MUCOPROTEIN EQUILIBRIUM

An extremely labile equilibrium between two groups of counter balancing, nonspecific factors appears to be constantly active in maintaining the serum mucoprotein level (Fig 3) The rapidity with which the level responded clinically to these factors is most clearly illustrated in a case of acute carbon tetrachloride (inhalational) poisoning, with hepatic, renal and pulmonary tissue damage Severe toxic hepatitis at the onset resulted in a reduction of serum mucoprotein (Fig 4 5) to levels of 30 mg per 100 cc (normal 48 to 75 mg) Within 6 days however as the jaundice subsided there was a sixfold rise in the level to 180 mg per 100 cc This rapid increase in mucoprotein concentrations appeared to reflect the tissue changes associated with protracted pulmonary edema bronchopneumonia and renal insufficiency The development of an increased concentration in a patient in whom only a few days previously the level had been subnormal appeared to be contingent upon the return of a functionally competent liver

The influence of urinary excretion of mucoprotein on the serum mucoprotein level has not been adequately investigated Normal human urine contains only several milligrams of mucoprotein per liter (37) A loss of mucoprotein through renal channels has been postulated to account for the reduced levels found in the nephrotic stage of glomerular nephritis (31) However no data have yet been presented to prove that excessive amounts of mucoprotein are lost in the urine in the presence of massive albuminuria In addition to a possible renal loss reduced mucoprotein levels in nephritic nephrosis might result from the alterations in hepatic and endocrine functions which often accompany the nephrotic syndrome The equilibrium of factors which determine the mucoprotein level in nephrotic syndromes due to amyloid renal disease appears to differ from that seen in nephritic nephrosis despite the fact that massive proteinuria occurs in both conditions The level did not fall in amyloid nephrotic syndromes secondary to inflammatory or neoplastic disease presumably because of the continuous release of mucoprotein from the focal tissue lesions initiating amyloid disease (secondary amyloidosis)

Figure 5 summarizes the effect of various diseases on the mucoprotein equilibrium In general the lesions which raise the level are those with an increased tissue response—proliferative inflammatory degenerative or traumatic—presumably mediated by a functionally

competent liver and adrenals The disorders which depress the level on the other hand are with few exceptions those of diffuse hepatocellular disease or pituitary adrenal insufficiency The mucoprotein-enhancing factors usually take precedence over the depressing factors since in such lesions as pneumonia and tuberculosis the level was usually elevated despite the presence of portal cirrhosis Massive hepatomegaly due to metastatic disease was almost invariably asso

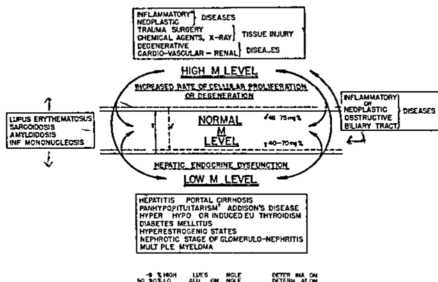


FIG 5—Summary of effect of various diseases on serum mucoprotein level On the right note that biliary obstruction did not result in a low level On the left are disorders which may produce either high normal or low levels Above and below are conditions which usually result in either a high or a low level

ciated with high levels Rarely in a slowly progressive neoplastic process in the liver as in chronic lymphatic leukemia an acute toxic (urethane) hepatitis induced depression of the mucoprotein level Acute inflammatory disease usually evoked a rapid rise whereas neoplastic growths resulted in a slow rise in the mucoprotein level Self limited or curable infectious processes were associated with a steady fall in the level to normal or in patients with portal cirrhosis to low levels Certain generalized disorders which often affect the liver and the endocrine glands and concomitantly induce a diffuse pathologic tissue response in other organs were found to result in either low normal or high mucoprotein levels depending on the predominant

foci of tissue change Included among such diseases (left side of Fig 5) were amyloidosis sarcoidosis infectious mononucleosis and lupus erythematosus The potentiality for bidirectional change in the level was apparently present in all patients and the direction and rate of change seemed to depend on the nature intensity and sequential development of the pathologic processes

HEPATOBILIARY DISEASES

The serum mucoprotein concentration drops in hepatocellular disease due to infectious hepatitis homologous serum hepatitis toxic (chemical) hepatitis and portal cirrhosis (25 27 29) This finding has been confirmed by Mandel and co workers (47) and by Ellison *et al* (48) Usually *the level fell progressively within the first 2 weeks* of persistent jaundice from either of the common forms of hepatitis (24 29) A serum concentration below the normal range was observed *in 88 per cent of our series of hospitalized patients with hepatitis in* the first serum obtained (24) These patients had a fairly severe form of disease Undoubtedly the percentage of reduced mucoprotein *levels would be smaller in very early or in mild cases of hepatitis* Employing a slightly wider range of normal values Mandel (26) found low levels in 80 per cent of his cases of hepatitis Toxic hepatitis due to urethane or carbon tetrachloride also was *associated* with reduced serum levels but hepatitis due to infectious mononucleosis only rarely resulted in subnormal levels The probable effect of concomitant inflammatory changes in lymph nodes pharynx and other extrahepatic foci was believed to be the reason why the muco protein concentration was not reduced in the latter form of hepatitis These extrahepatic tissue responses in mononucleosis raised the level or prevented it from falling to the usual low range seen in the more common forms of hepatitis (29)

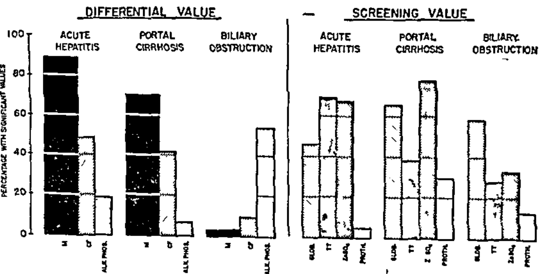
Of the small group of patients with infectious hepatitis or homol ogous serum hepatitis who failed to show low mucoprotein levels in the first serum studied approximately two thirds had clinically obvious coincidental extrahepatic inflammatory or neoplastic *diseases* (24) The other third or about 5 per cent of the patients with hepatitis usually with mild transient jaundice failed to show a low level and followed the course and clinical findings consistent with a *mild form* of cholangiolitic hepatitis " In the more protracted cases of cholangiolit

ic hepatitis low levels usually developed within 2 to 3 weeks after the onset of jaundice *Amebic infection (24 27 47) hepatitis due to* infectious spirochetosis (47) and hemolytic jaundice of varied etiology (24 27 47) were not associated with the low serum mucoprotein concentrations usually seen in infectious or homologous serum hepatitis

In our group of 89 hospitalized patients with portal cirrhosis the mucoprotein concentration in the first specimen obtained was low in about 70 per cent In the series reported by Mandel and co workers (47) analyzed with a wider range of normal values 60 per cent had low values There was also a preponderance of low values in a small number of cases of "cardiac cirrhosis" The values were normal or high in 4 patients with hemochromatosis and in 8 with fatty liver degeneration and massive hepatomegaly When portal cirrhosis was coincidentally associated with self limited or curable inflammatory disease such as pneumonia the level often fell abruptly to the sub normal uncomplicated cirrhotic" range (Fig 4) A slowly rising level was usually found in cirrhotic patients with hepatoma or other progressive neoplastic disease

The occurrence of normal or high mucoprotein levels in various forms of acute subacute or chronic biliary obstruction was in distinct contrast to the usually reduced concentrations in most patients with hepatocellular disease Reduced levels were found in less than 3 per cent of more than 400 patients with obstructive jaundice studied by three separate investigators (25 47 48) Even in the most advanced stages of biliary cirrhosis the mucoprotein concentration did not fall to the low levels seen in portal cirrhosis (27 29) The high concen trations in obstructive jaundice were found predominately in patients with acute cholangitis acute cholecystitis acute pancreatitis or ad vanced carcinoma of the pancreas whereas in small ampullary or pancreatic carcinomas or in the initial stages of common duct stone with minimal cholangitis the mucoprotein values were normal

A comparison of the mucoprotein determination with established liver diagnostic tests has yielded favorable results as reported by *several investigators (25 47 48) They found that* in differentiating medical from surgical jaundice the former particularly when indicat ing a low level was equal to or better than the results of cephalin flocculation thymol turbidity alkaline phosphatase albumin–globulin ratio prothrombin time or zinc sulfate turbidity determinations The



	TEST	VALUE CONSIDERED SIGNIFICANT
M	SERUM MUCOPROTEIN	< 48 mg / ♂ < 40 mg / ♀
CF~	CEPHALIN FLOCCULATION	> 2+
ALK. PHOS	ALKALINE PHOSPHATASE	> 24 KING ARMSTRONG UNITS > 12 BODANSKY UNITS
GLOB	SERUM GLOBULIN	> 32 gm /
TT	THYMOL TURBIDITY	> 70 UNITS
$ZnSO_4$	ZINC SULPHATE TURBIDITY	> 90 UNITS
PROTH	PROTHROMBIN TIME	< 50 /

✓Fig 6—Comparison of simultaneous determination of serum mucoprotein concentration and a battery of liver diagnostic tests commonly used in differential diagnosis of jaundice. Values are those observed from the first serum specimen obtained for study from hospitalized patients

apparent statistical superiority of the mucoprotein determination over the best two of the older procedures—the cephalin flocculation and the alkaline phosphatase—is illustrated in Figure 6 In the first serum specimen obtained for study low mucoprotein levels were found in 77 per cent of the cases of hepatogenous jaundice but only in 3 per cent of obstructive jaundice cases Simultaneous determination of the alkaline phosphatase showed 55 per cent with markedly elevated levels (> 24 K A units) in the obstructive jaundice group versus 15 per cent in hepatogenous jaundice Comparison of the cephalin flocculation figures revealed 45 per cent with positive values (> 2+) in hepatogenous jaundice versus 8 per cent in biliary obstructive disease

Although the finding of a low serum mucoprotein level clearly favored the diagnosis of hepatogenous jaundice the significance of normal or elevated levels in jaundiced patients depended upon circumspect evaluation of the various factors involved A rising level in the presence of continuing jaundice was usually associated with biliary obstruction In contrast a falling level with persistent jaundice almost always signified hepatocellular disease Serial mucoprotein determinations were therefore particularly useful in those cases in which clinical impressions and mucoprotein determinations did not initially coincide Such serial determinations often accelerated a complete and thorough check in perplexing cases by pointing to the need for definitive diagnostic procedures such as special roentgen studies liver aspiration biopsy or laparotomy While the serum mucoprotein level could in no true sense be considered a liver function test reflecting at all times an equilibrium based on nonspecific factors which in the jaundiced patients could be influenced upward or downward (Figs 2–4) determination of the serum concentrations nevertheless yielded considerable information useful for the clinical management of conditions involving jaundice

Clinically it was of considerable interest that the development of metastatic hepatomegaly with virtual replacement of the liver was not associated with any tendency of the mucoprotein level to fall into a misleading range of values whereas the results of the cephalin flocculation albumin–globulin ratio or other determinations often suggest primary hepatocellular disease On the contrary the serum mucoprotein content in metastatic hepatomegaly was almost invariably high when the patient was first seen and continued to increase as the disease progressed On the basis of this observation, the finding

of a low level in a patient with hepatomegaly of obscure origin virtually excluded the likelihood that the hepatomegaly was due to metastases from an extrahepatic primary site

No reports on the potential usefulness of the serum mucoprotein value in the evaluation of posthepatitis syndromes or of hepatitis carriers have yet been published although preliminary data on the former (24) appear to warrant further investigation

Since a relatively small number of clinical conditions was associated with reduction in serum mucoprotein concentrations [1] the correlation of clinical diagnoses with the finding of low levels was studied in a large series of hospital and clinic patients About half of all patients with low values had clinically diagnosed hepatitis or portal cirrhosis another 10 per cent had probable hepatocellular disease (incompletely *investigated cases*) *about 30 per cent had nephrosis myeloma* or pituitary-adrenal disorders the remaining 10 per cent did not readily fit into any of these categories Thus there was more than a 50 per cent chance that the random finding of a low mucoprotein concentration would be associated with hepatocellular disease By the simple exclusion of cases with proteinuria this relationship to hepatocellular disease became even more definite The low level would seem to represent a fairly reliable guide to the presence of clinically evident hepatic or endocrine insufficiency High serum mucoprotein levels on the other hand were found to occur in so many clinical conditions that their chief value like an increased sedimentation rate appeared to be in following the course of various diseases or in screening for organic disease Only in the diagnosis of jaundice and hepatomegaly did an increased level have any true differential significance

RHEUMATIC COLLAGEN AND CARDIOVASCULAR DISEASES

According to Kelley (35) and others (27) at least 80 per cent of patients with active rheumatic fever may be expected to have an increased serum mucoprotein concentration The degree of rheumatic activity as determined by the sedimentation rate *and by clinical* manifestations correlated well with degree of increase in serum mucoprotein content In patients not receiving ACTH the level dropped to normal about as fast as the sedimentation rate but with ACTH therapy of active rheumatic fever the mucoprotein level remained elevated long after the sedimentation rate and hyaluronidase-inhibitor level

had returned to normal Since ACTH is known to stimulate the maintenance of a high mucoprotein level it cannot be considered a reliable guide to rheumatic activity as such in ACTH treated patients Furthermore the mucoprotein level fails to reflect the rheumatic tissue response specifically so that various thrombotic (27) embolic and other cardiovascular complications not necessarily related to rheumatic activity can also produce marked fluctuations in the levels A high level appeared to warrant careful evaluation in rheumatic patients although it could not be considered strong evidence of rheumatic activity unless other pathogenetic factors in the patient had been excluded Patients with high levels usually but not always had increased values for C-reactive protein (24) In some patients hyaluronidase inhibitor values fluctuated independently of mucoprotein concentrations (32) Thus although mucoprotein C-reactive protein, and hyaluronidase inhibitor usually responded in a more or less parallel manner as "acute phase" α-globulin reactants (24) in a small group of patients the trend of these presumptive indices of rheumatic activity varied independently

Increased mucoprotein concentrations were also found in most patients with active rheumatoid arthritis but in only 50 per cent of patients with disseminated lupus erythematosus (27) The rapid development of increased levels after acute episodes of myocardial infarction pulmonary infarction and congestive heart failure was further evidence of the responsiveness and nonspecificity of the serum mucoprotein level in cardiovascular rheumatic and collagen disorders

INFECTIOUS DISEASES

Increased serum mucoprotein concentrations were observed in over 90 per cent of patients with such acute infectious diseases as pneumonia, enteritis, cellulitis, tuberculosis, and brucellosis The principal common infectious diseases in which there was no consistent increase in levels were infectious mononucleosis infectious hepatitis the common cold and mild grippe like syndromes The values were usually normal or high in mononucleosis usually low in hepatitis and indefinite in mild viral diseases In subacute or chronic inflammatory diseases such as endocarditis ileitis colitis sinusitis diverticulitis bronchiectasis and tuberculosis the over all incidence of high values was about 75 per cent with elevated levels occurring predominantly in the more active lesions Hepatocellular disease with impaired liver func

tion may have been the reason why a small number of patients had no significant increase in mucoprotein levels despite the obvious presence of extrahepatic inflammatory disease

In most patients with infectious or inflammatory disease the level did not appear to warrant any other practical consideration than would have been attributed to an elevated sedimentation rate The response of the level after treatment seemed to have some importance in detecting underlying hepatocellular disease in these patients

NEOPLASTIC DISEASE

The serum mucoprotein level was of no real value in the discovery of early localized cancer On the contrary the levels in only 50 per cent of a large group of patients with head or neck cancer were increased after they were hospitalized for definitive treatment. Advanced visceral cancer or lymphoid neoplasms were associated with high levels in about 80 per cent of hospitalized patients A still greater incidence of increased levels was found in metastatic hepatomegaly which may have some significance in its differentiation from hepatomegaly due to portal cirrhosis

Multiple myeloma was the only disseminated neoplastic disease which was associated with a reduced mucoprotein level the decrease was found in about half of a large series of cases with most of the rest having normal values Except in the multiple myeloma cases a low concentration was observed in only 3 per cent (13 cases) of 270 patients in our initial series of hospitalized patients with neoplastic disease 11 of them showed obvious clinical evidence of either hepatocellular failure or endocrine dysfunction Included in this group of 11 were a few instances of each of the following panhypopituitarism due to craniopharyngioma portal cirrhosis with hepatoma urethane hepatitis with chronic leukemia and postorchiectomy estrogen control of advanced prostatic carcinoma Apparently a low serum mucoprotein level whether in a patient with neoplastic or non neoplastic disease was reasonably good evidence of the presence of hepatic and/or endocrine deficiency

RENAL DISEASES

Acute glomerular nephritis (27) and the terminal uremic stages of glomerular nephritis pyelonephritis and nephrosclerosis were con

sistently associated with high levels of serum mucoprotein This finding contrasted with that of a frequent subnormal mucoprotein content in most patients in the nephrotic stage of glomerulonephritis (27 30) Kelley (31) reported that among 20 children with nephrosis 17 had reduced levels In a similar series of ours including adults and children with nephrosis about 80 per cent had low values (24 27) During the transition from nephrosis to the terminal nephritic stage the level slowly increased until high values were reached Even in patients with nephrosis in whom low mucoprotein levels were presumably the result of loss by way of the urine there was an equilibrium of factors which could cause rapid fluctuation in mucoprotein values Thus acute infections induced temporarily increased levels in cases of nephrosis (24) as well as in portal cirrhosis In a small group of patients with the nephrotic syndrome due to secondary amyloidosis serum mucoprotein levels were not reduced despite massive proteinuria These observations might indicate that the inflammatory or neoplastic foci causing the amyloidosis were responsible for the maintenance and in some instances for an increase in mucoprotein even in the presence of a nephrotic syndrome A decrease in mucoprotein content appeared to be consistent with the primary renal nephrotic syndrome (glomerulonephritis) upon further study it may provide some differential basis for ruling out amyloidosis in nephrosis without uremia This singular difference in the serum protein patterns of various etiologic types of nephrosis further suggested the possibility that chronic glycoproteinemia and with it mucoproteinemia may be a factor in the tissue deposition of the abnormal carbohydrate–protein complexes in amyloid disease

ENDOCRINE AND METABOLIC DISEASES

Endocrine disease depressed the serum mucoprotein level primarily in patients with pituitary or adrenal insufficiency and to some extent in patients with thyroid disorders or diabetes mellitus (27) Subnormal values were found in at least three fourths of patients with Addison s disease or panhypopituitarism (24 27) In none of these patients with pituitary–adrenal failure was there any of the usual clinical or laboratory evidence of primary hepatocellular disease Low levels were found in about 30 per cent of a large group of clinic patients with various thyroid disorders Most of the group with low mucoprotein values had hyperthyroidism accompanied by clinical evidence of

hepatocellular dysfunction The remainder had myxedema more frequently of the pituitary type The basal metabolic rate therefore, was not directly related to the observed mucoprotein values In a group of diabetic patients mainly ambulatory and with diabetes under control without acute cardiovascular or renal complications about 15 per cent had low mucoprotein levels and 10 per cent had high values The low levels presumably reflected the presence of hepatocellular disease while the high levels perhaps indicated the presence of various slowly developing inflammatory or degenerative processes

These clinical findings in endocrine disease were consistent with experimental data which indicated that an adrenal mechanism is involved in the maintenance of serum mucoprotein levels (24 28) There are no reports on mucoprotein concentrations in Addison s disease secondary to tuberculosis or neoplasm but it seems likely that an active inflammatory or neoplastic process could overcome the tendency to lowered levels in pituitary adrenal insufficiency as may be seen when such complications occur in patients with hepatocellular insufficiency An increase in mucoprotein levels as a result of cortisone therapy in Addison s disease or of ACTH therapy in panhypopituitarism have been observed in several instances Since human urinary gonadotropin is a mucoprotein serum mucoprotein was investigated for possible gonadotropic properties with negative results (24) Whether any possible hormonal effect of mucoprotein is blocked by denaturation during its isolation from serum is not known In patients with endocrine dysfunction the mucoprotein level would appear to represent a relatively labile equilibrium based on clinically important, but nonspecific factors A definitely low value might help in the evaluation of patients with endocrine disease

SUMMARY AND CONCLUSIONS

The serum mucoprotein determination represents a simple quantitatively reproducible procedure It can be routinely performed in most clinical laboratories if the derived data are found of definite clinical value to the practicing clinician The serum content of mucoprotein may rise or fall in response to virtually the entire gamut of human organic diseases The vast majority of patients with the common infectious inflammatory neoplastic traumatic cardiovascular and rheumatic diseases regularly manifest an increase in the mucoprotein con

centration Nevertheless there would seem to be little reason to prefer the mucoprotein determination to such an easily performed procedure as the sedimentation rate for following the course of these disorders Bidirectional fluctuations in mucoprotein values as a result of changing organic lesions may occur with surprising rapidity In addition casual or improper handling of blood in the laboratory may result in a false impression of fluctuating levels These factors make it unwise to use mucoprotein determination as a routine laboratory aid in differential diagnosis

The usefulness of mucoprotein determinations seemed to be confined to certain types of diagnostic or therapeutic problems by and large in conditions in which a low level or absence of a low level was significant These included the differential diagnosis of *(1)* hepatogenous versus obstructive jaundice *(2)* hepatomegaly of obscure origin *(3)* nephrotic syndromes *(4)* endocrine (pituitary adrenal) insufficiency and *(5)* suspected organic disease of unknown etiology

The serum mucoprotein is one of the simplest of the "acute phase" alpha globulin reactants available for quantitative study by clinical laboratories Its determination may be included as one of the components in a battery of simple procedures suitable for detection of the abnormal globulin distribution patterns frequently found in sarcoidosis nephrosis lupus erythematosus myeloma and hepatobiliary diseases Whenever the mucoprotein level was employed as a laboratory aid it was necessary to pay close attention to the multivalent factors which might influence the level in the individual patient at any time Despite the lability nonspecificity and potential for bidirectional change the single and serial determination of mucoprotein concentrations in jaundiced patients appeared to have practical merit in differentiating medical from surgical jaundice It was as useful, or better than the alkaline phosphatase cephalin flocculation or other commonly employed liver function tests

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Advances in Physiology of Clinical Disorders of the Adrenal Cortex

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INTEREST IN the physiology chemistry and diseases of the adrenals is steadily increasing The great impetus for this development can no doubt be ascribed to the new technics of study which have led to concepts inconceivable 10 years ago The technic of paper chromatography developed by Zaffaroni (71) Bush (6) and others makes the identification of minute quantities of adrenal steroids relatively simple Hechter Pincus and their collaborators (20) at the Worcester Institute have evolved methods of adrenal perfusion by which the biologic precursors of certain adrenal steroids can be determined Clinically the use of cortisone introduced by Hench and his collaborators (24) soon followed by the introduction of ACTH have so enlarged the scope of steroid therapy that practically every subspecialty of internal medicine has been affected With the availability of replacement therapy adrenalectomy has begun to be used in the treatment of certain adrenal diseases The addisonian like state which this procedure may produce has provided clinical material for study All these developments have made possible tremendous strides in our knowledge of the adrenal cortex and the steroids A better understanding of the chemistry and biologic activity of the adrenal steroids has led to a better comprehension of adrenal disease and the diagnosis and treatment of such diseases now rest on a biochemical and physiologic basis Much still remains to be done in elucidating the biosynthesis and secretion of the adrenal steroids and in studying all the physiologic activities under steroidal control

The literature on this subject is so extensive that references here have been limited so far as possible to reviews

CHEMISTRY OF ADRENAL STEROIDS —The chemistry of the adrenal cortex is extremely complex as evidenced by the fact that 31 different steroids have been isolated from adrenal tissues In addition urinary steroids have been found which are probably of adrenal origin The latter are degradation products or metabolites of the steroids secreted by the adrenal and/or the gonads and placenta These three organs appear to be the only ones responsible for steroid secretion The reader is referred to extensive reviews by *Lieberman and Teich (37)* and by *Dorfman* and Ungar (11) on the chemistry and metabolism of these steroids

The steroids isolated from adrenal tissue can be classified according to their chemical composition This is most easily done according to the number of carbon atoms

I C 21 or pregnane series subdivided according to number of oxygen atoms more important ones follow

	ALPHABETICAL REICHSTEIN	DESIGNATION KENDALL
C 21-O_5 steroids		
17 hydroxycorticosterone	M	F
17 hydroxy 11-dehydrocorticosterone (cortisone)	Fa	E
aldosterone or electrocortin		
C 21-O steroids		
Corticosterone	H	B
11 dehydrocorticosterone		A
17 hydroxydesoxycorticosterone	S	
C 21-O steroids		
17 hydroxyprogesterone		
desoxycorticosterone (DOC)	Q	
C 21-O steroids		
progesterone		

II C-19—androstane or etioallocholane series
androstanediol-3(β) 11(β) one 17
adrenosterone
Δ^4 androstendione-3 17

III C 18 series
estrone

The structural formulas of the more important steroids are shown in Figure 1

The basis for the nomenclature of steroids has been amply reviewed by Reichstein and Shoppee *(48)* and by *Mason (41)*

BIOSYNTHESIS OF STEROIDS —The previously held concept of immutability of steroids has been amply disproved the past few years Hechter Pincus and their collaborators *(20–22)* at the Worcester Foundation have devised technics for perfusing surviving adrenal tissue have

isolated certain steroids from these perfusates and have demonstrated that one can be converted by the surviving adrenal tissue into another This is accomplished primarily by a series of hydroxylations at the C 11 C 17 and C 21 positions (18 19 23 40) In this manner when progesterone is perfused through surviving adrenal tissue corti

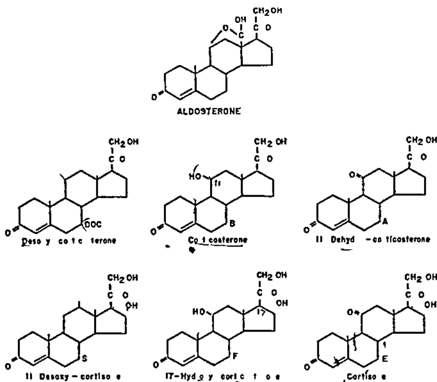


Fig 1 —The more important adrenal cortical steroids

costerone and hydrocortisone are isolated Similarly desoxycorticosterone can be converted to corticosterone

Hechter and Pincus (22) have found that perfusion of C^{14} cholesterol through adrenal tissue achieves the synthesis of radioactive hydrocortisone and corticosterone In addition C^{14} acetate perfusion results in similar genesis of corticosteroids Hechter and his collaborators claim that the utilization of the two carbon fragments in this biosynthesis does not necessarily involve cholesterol as an obligatory intermediary Consequently it is possible that although cholesterol can be

an intermediary in the synthesis of hydrocortisone and corticosterone alternate pathways are present and cholesterol can be by passed (Fig 2)

In cholesterol the "B" ring is unsaturated whereas in the active adrenal steroids it is the "A ring that is unsaturated The conversion of cholesterol to Δ^5 pregnenolone is therefore postulated Samuels (44 54) and others have presented evidence for a steroid 3(β)-ol dehydrogenase in adrenal tissue as well as in testes placenta and

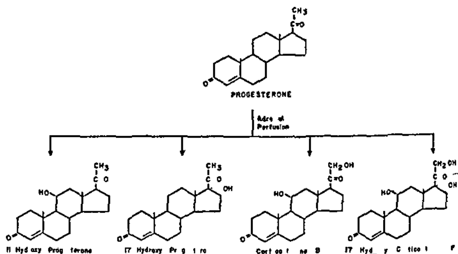


Fig 2 —Types of hydroxylation of progesterone by surviving adrenal tissue

ovary This enzyme system can account for the conversion of preg nenolone to progesterone

Hechter has also pointed out that the point of action of ACTH on corticosteroidogenesis is at a very early step in the process of steroid synthesis The addition of ACTH to adrenal perfusates increases the yield of corticosteroids 25 fold when cholesterol is used as the starting material whereas with progesterone as the starting steroid there was only a 20 to 25 per cent increase

This work was greatly facilitated by the development of paper chromatography together with methods for the identification of minute amounts of steroid Zaffaroni Bush and other investigators have de veloped these micromethods of identification together with the use of ultraviolet and especially infra red spectrophotometry

The adrenal cortex apparently differs from other glands in that

more than one steroid is secreted The evidence would indicate that hydrocortisone is the most important C-21 steroid but corticosterone is found as well In addition it has been demonstrated that the adrenal cortices of various species secrete different C-21 steroids Table 1 lists the various ratios of hydrocortisone to corticosterone in various species An adrenal androgen has also been identified in human adrenal vein blood It is noteworthy that hydrocortisone is the most important adrenal steroid secreted by man and monkey whereas in rodents corticosterone is more important It has also been shown that in the rat

TABLE 1 —RATIO OF CONCENTRATION OF HYDROCORTISONE TO CORTICOSTERONE IN ADRENAL VEIN BLOOD OF VARIOUS SPECIES (13)

SPECIES	RATIO	SPECIES	RATIO
Man	10	Cat	4–6
Monkey	20	Ferret	1.5
Sheep	1	Rabbit	<0 05
Dog	1.2–20	Rat	<0 05

prolonged ACTH stimulation may change the ratio so that hydrocortisone becomes the more important steroid

PHYSIOLOGIC ACTIVITY OF ADRENAL STEROIDS —In this respect, too the adrenal is peculiar for not only does it secrete several hormones (steroids) but these steroids have different physiologic activities some of which can be predicted in part at least, from the structure of the steroid

C 21 11 desoxy steroids —Desoxycorticosterone, 17 hydroxydesoxycorticosterone or compound S and aldosterone are steroids with similar physiologic effects acting primarily on salt and water metabolism It is still not clear whether desoxycorticosterone is a normal constituent of adrenal tissue Aldosterone is the most recently isolated and identified adrenocortical steroid Before these steroids were identified (17 58) it had been known for many years that after isolation of all the known steroids of the adrenal cortex the remaining, so-called "amorphous fraction" retained great salt and water activity It is from this fraction that aldosterone has been isolated and has now been shown to have 10 to 30 times the biologic activity of desoxycorticosterone

11 Oxygenated steroids —The steroids containing an oxygen or hydroxy group on carbon 11 are characterized by the fact that their

effect is primarily on carbohydrate and protein metabolism with only minimal effects (milligram per milligram) on electrolyte metabolism The differences in the biologic effects of these two groups of substances are demonstrated in the Table 2

C 19 steroids —The C 19 steroids isolated from the adrenal glands are androgens and their biologic effects appear to be similar to those of testosterone 17(β) Hydroxyprogesterone has also been isolated but apparently this steroid is a mild androgen with no progestational activity

Progesterone has been isolated and its effects upon the endometrium

TABLE 2 —DIFFERENCES IN BIOLOGIC ACTIVITY OF ADRENAL STEROIDS BY VARIOUS ASSAYS

STEROID	LIFE MAINTENANCE	SODIUM RETENTION	LIVER GLYCOGEN	ANTI INSULIN	EOSINOPHIL FALL
Desoxycorticosterone (DOC)	++++	++++	0	0	0
Corticosterone	+	+	++	++	0
Cortisone	+	+	++++	++++	++++
Hydrocortisone	+	+	++++	++++	++++
Aldosterone	10–30 × DOC	10–30 × DOC	++	++	++

are known Estrone has been isolated from adrenal tissue and of course its biologic effect is estrogenic

CONTROL OF ADRENOCORTICAL SECRETION —Smith (59) in 1930 was the first to demonstrate unequivocally the control of the adrenal cortex by the pituitary by showing the dependence of the adrenal cortex upon the trophic action of the anterior lobe of the pituitary On the other hand Greep and Dean (16) have claimed that in rats the adrenal secretion of the minerocorticoids is independent of pituitary control Nurnberger and Korey (43) have summarized some of the clinical experiences in the surgical treatment of patients with chromophobe adenoma and it would appear that pituitary control of the adrenal is more complete in man than in the rat

The adrenocorticotropic hormone (ACTH) of the anterior lobe of the pituitary has been isolated in very pure form by Li Hays Morris and Astwood and his associates (*3 9 49*) *At present* the question whether there is only one or several types of ACTH is a matter of dispute (36 50) In all probability the ACTH molecule is a polypeptide but its exact chemical nature has not been ascertained

Administration of ACTH to the experimental animal is followed by an almost immediate fall in the ascorbic acid and cholesterol contents of the adrenal Since technically the determination of ascorbic acid content is simpler than that of cholesterol the former has been used for the assay Apparently there is some discrepancy between the results obtained by assay on the hypophysectomized rat and the therapeutic results in man attempts are now being made to assay this substance in man

When an intact animal is exposed to any sort of stress—toxin trauma heat hemorrhage—the ascorbic acid content of the adrenal is almost immediately depleted A similar stress suffered by an animal deprived of its pituitary gland has no effect on the adrenal ascorbic acid Since the effects of stress and ACTH are quite similar it is postulated that in the normal animal exposure to stress causes an immediate secretion of ACTH in the hypophysectomized animal this is of course impossible (56)

The mechanism by which a nonspecific stress stimulates the pituitary gland to secrete ACTH is not yet clear It has been proposed that epinephrine is the common denominator for all stress causing secretion of ACTH presumably through a hypothalamic–pituitary system On the other hand there is equally good evidence which seems to indicate that ACTH secretion depends upon the level of circulating corticoids Sayers (56) theory is that stress results in an increased utilization of the circulating adrenal hormone This decreases the level and causes the pituitary to secrete more ACTH which in turn stimulates the adrenal cortex to maintain homeostasis A review by Long (39) summarizes all the mechanisms postulated

The immediate response of the pituitary–adrenal axis to stress has been called the alarm reaction by Selye (57) and he has developed a theory of the role of ACTH and later of growth hormone in the etiology of certain diseases of adaptation Since Selye first introduced his concept of the adaptation syndrome many investigators have worked to uncover evidence to support or contradict it (45a) Ingle (25a) on the other hand has shown that certain of the physiologic manifestations of stress can occur in the adrenalectomized animal receiving a constant dose of adrenocortical extract his theory is that the adrenal plays a permissive role in stress In brief a certain amount of circulating adrenal hormone is necessary for the physiologic reactions of stress to become manifest Nevertheless these re

actions can occur without an excessive production of adrenal steroids

ASSAY OF ADRENAL FUNCTION IN MAN—At present, there is no one test which in itself will adequately show whether the adrenal gland is functioning or not As in other clinical states several tests must be done and evaluated before a conclusion can be reached

Urinary 17 ketosteroids—The so called Zimmerman reaction with *m dinitrobenzene is not an absolutely specific test for steroidal ketones* it can be made more specific by separating the Zimmerman reactive chromogens by means of chromatography and identifying the steroids This long and complicated technic requires expensive apparatus in addition to a professional chemist In view of the nonspecificity of the urinary 17 ketosteroids the values are only an aid in evaluating adrenal function The 17 ketosteroids are low not only in Addison s disease and in hypopituitarism but also in many other chronic diseases endocrine *or otherwise Normal men excrete between 10 and 20 mg per day* women between 6 and 15 mg per day

The more commonly encountered 17 ketosteroids found in normal urine are etiocholanolone androsterone dehydroisoandrosterone or dehydroepiandrosterone 11 ketoetiocholanolone and 11 hydroxy androsterone

Urinary corticoids—In the past few years methods have been developed for measuring the C 21 steroids and their degradation products in the urine However as has been recently learned these steroids are conjugated with glucuronic acid and appear as glucuronides in the urine There is no complete agreement on the best method of hydrolyzing these conjugates so that as with the urinary total neutral 17 ketosteroids the methods are open to the criticism of nonspecificity and of incomplete hydrolysis The two most popular methods are the formaldehydogenic which measures the amount of formaldehyde liberated from the side chain and the Porter Silber method with phenyl hydrazine which measures the glycerol side chain The latter presumably is more specific for 17 hydroxylated corticoids These values are low in Addison s disease and in secondary adrenal disease due to hypopituitarism but they too may be low in many other chronic diseases The values vary with the methods of hydrolysis and colorimetry employed

The corticosteroids which have been isolated from the urine of normal individuals are tetrahydrocortisone tetrahydro hydrocortisone hydrocortisone and cortisone The 11 oxygenated 17 ketosteroids are probably metabolites of hydrocortisone

Plasma corticoids—Recently it has become possible to measure the 17 hydroxycorticoids in plasma mainly as a result of the work of Nelson and Samuels (42) and of Bayliss and Steinbeck (5) Apparently the values obtained are somewhat more specific than the urinary values In normal men and women the values vary between 5 and 25 µg per liter of plasma

ACTH test—Since the urinary 17 ketosteroids and corticoids may be low in any chronic disease the values in themselves are not diagnostic of adrenal insufficiency However in nonspecific chronic disease the adrenals will respond when stimulated with exogenous ACTH and an ACTH test was devised to determine the reactivity of the adrenal cortex The urinary 17 ketosteroids corticoids plasma corticoids and circulating eosinophils may be used as indices After suitable control periods 25 units of ACTH is given intravenously over a 4 hour period on 2 successive days or the ACTH may be given intramuscularly at 6 hour intervals for 2 to 3 days In our experience the former method appears to be more sensitive If the adrenal cortex can respond to stimulation a substantial increase in the ketosteroids and corticoids should be detectable and a 50 per cent increase in the plasma corticoids at the same time there is a fall of over 50 per cent in the circulating eosinophils The eosinophil test is the simplest to perform but is the least reliable It would appear that far too much reliance has been placed on this test (12 15 21 51)

Water loading tests—In the absence of functioning adrenal tissue the kidney cannot excrete a water load and water intoxication may occur Several tests were devised by Kepler and his colleagues (52) and more recently Soffer (61) has proposed a modification of these methods The tests ascertain the time required to excrete a certain percentage of an administered quantity of water The adrenalectomized or adrenal deficient patient will retain the water longer than will the normal individual The normal response depends upon the presence of cortisone or hydrocortisone (44) and not desoxycorticosterone as is commonly thought.

Salt deprivation or salt withdrawal test—It is probably the most rigorous test of adrenal function Even this test, however is nonspecific since an abnormal response is also obtained in severe renal disease which has led to serious errors of diagnosis in normotensive chronic pyelonephritis On a low salt diet, the serum sodium level falls in the patient with adrenal insufficiency he will do poorly lose weight, actually become nauseated and vomit and go into an adrenal crisis

within a few days *This test is dangerous and should only be done if* the patient can be kept under close observation in a hospital Obviously prolonged rigid salt restriction will result in a fall in the serum sodium level in individuals with normal adrenal function Consequently the salt deprivation diet used for testing adrenal function should contain about 1 5 Gm of sodium chloride

CLINICAL ASPECTS

HYPOADRENALISM

The classic features of weakness weight loss anorexia nausea vomiting, and pigmentation are well known signs and symptoms of Addison s disease and require little comment It should be remembered *that many of these symptoms and signs are common to other disorders* and consequently are not diagnostic of adrenal insufficiency Only combined pigmentation of skin *and* mucous membranes is pathognomonic The diagnosis of hypoadrenalism may be quite apparent or very difficult to establish Certainty of diagnosis is of utmost importance since the diagnosis of Addison s disease commits an individual to lifelong therapy and the mental hazard of constant vigilance to the dangers of stress while failure to recognize a treatable disorder causes prolonged invalidism or death Whether partial adrenal insufficiency exists or whether there are individual variations in the degree of adrenal function are questions which cannot be answered at present However on the basis of animal experiments in which minute amounts of adrenal tissue suffice to maintain the animals in normal status it is difficult to believe that partial or relative adrenal insufficiency can exist for long In the final analysis the diagnosis of adrenal insufficiency is based upon laboratory confirmation of the clinical impression and in this way little evidence of continued mild hypoadrenalism is obtained

ETIOLOGY OF PRIMARY ADRENAL INSUFFICIENCY —In about 50 per cent of the patients with primary adrenal insufficiency the adrenals are destroyed as a result of tuberculosis the rest have what is called primary atrophy of the adrenal the cause of which is unknown Another cause of adrenal insufficiency the iatrogenic has had to be considered in recent years following bilateral adrenalectomy on patients with metastatic carcinoma of the breast and prostate hypertension Kimmelstiel Wilson syndrome and Cushing s syndrome

PHYSIOLOGIC AND CHEMICAL MANIFESTATIONS OF HYPOADRENALISM — *Pigmentation* —Although most of the signs and symptoms of adrenal

insufficiency have been produced experimentally in animals there is no experimental counterpart of the pigmentation of skin and mucous membranes which is so characteristic of Addison s disease Apparently its existence can be correlated with the postulated levels of circulating ACTH in the blood which in Addison s disease are elevated It has also been demonstrated that in certain patients prolonged continuous administration of a commercial ACTH preparation may cause pigmentation similar to that found in Addison s disease whereas cortisone does not have that effect It is possible that not ACTH itself but a contaminant the melanophore expanding hormone is responsible for the pigmentation The latter hormone has an effect upon the melanophores in amphibia and fish If this is a separate hormone from ACTH apparently its secretion by the pituitary is inhibited by cortisone administration

Salt and water metabolism —In brief this metabolic defect in adrenal insufficiency is due to the failure of the reabsorption of sodium in the renal tubules and an increased loss of sodium in sweat and feces On the other hand renal absorption of potassium is increased and potassium is withdrawn from the tissues This results in dehydration which is manifested by hemoconcentration The fall in blood pressure characteristic of this condition may be related to this phenomenon

Desoxycorticosterone is the most effective steroid available for correction of this pathologic mechanism The recently discovered steroid aldosterone (electrocortin) considered to be 10 to 30 times more potent than desoxycorticosterone is not commercially available at present It has also been claimed that 9 α fluorohydrocortisone is as effective as desoxycorticosterone in salt and water metabolism Sodium chloride must be added to the regimen in order to provide a substrate for the mineralocorticoid to work The desoxycorticosterone requirement in patients with Addison s disease varies with the individual and must be worked out in much the same way as for insulin in diabetes

Carbohydrate and protein metabolism —In the adrenalectomized animal or the patient with Addison s disease gluconeogenesis from protein is decreased and there is apparently an increased oxidation of the carbohydrates at the periphery These two factors result in a low blood sugar and low hepatic glycogen stores The 11 desoxysteroids have very little effect on this phase of Addison s disease while cortisone or hydrocortisone are usually effective

TREATMENT OF ADDISON S DISEASE —As in diabetes mellitus the treat

within a few days This test is dangerous and should only be done if the patient can be kept under close observation in a hospital Obviously prolonged rigid salt restriction will result in a fall in the serum sodium level in individuals with *normal adrenal function* Consequently the salt deprivation diet used for testing adrenal function should contain about 1 5 Gm of sodium chloride

CLINICAL ASPECTS

Hypoadrenalism

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Etiology of primary adrenal insufficiency —In about 50 per cent of the patients with primary adrenal insufficiency the adrenals are destroyed as a result of tuberculosis the rest have what is called *primary* atrophy of the adrenal the cause of which is unknown Another cause of adrenal insufficiency the iatrogenic has had to be considered in recent years following bilateral adrenalectomy on patients with metastatic carcinoma of the breast and prostate hypertension Kimmelstiel Wilson syndrome and Cushing s syndrome

Physiologic and chemical manifestations of hypoadrenalism — *Pigmentation* —Although most of the signs and symptoms of adrenal

on electrolyte balance however is difficult to foretell since this can vary from patient to patient Figure 3 shows the markedly dissimilar responses of 2 patients with Addison s disease both receiving cortisone orally In patient E L cortisone maintained the patient s positive salt metabolism whereas patient R S on a dose of 200 mg per day continued to lose sodium in the urine and show a decrease in serum sodium of almost 10 mEq (34) Consequently desoxycorticosterone must be added to the regimen of most patients This may be administered intramuscularly daily or in the form of the long acting desoxy corticosterone trimethyl acetate about once a month it may also be administered as subcutaneously implanted pellets

The enhancing effect of large doses of cortisone on tuberculosis has been noted (8) It should therefore be used with great caution and in minimal doses in those patients in whom Addison s disease is due to tuberculosis of the adrenals Hypertension may occur with cortisone therapy but is more likely when desoxycorticosterone and salt are used in excess

Whether the patient is being given cortisone alone or desoxycorticosterone sodium chloride must be added to the regimen When the patient shows signs of excessive salt retention the amount of added salt can be very easily reduced

TREATMENT OF ADRENAL CRISIS —The clinical symptoms of a crisis may vary widely Fever often of extreme degree even in the absence of any demonstrable cause is common Shock may be present The patient s mental state may vary from normal to that of coma Onset of the crisis may be sudden or gradual When vomiting has been prominent, dehydration as evidenced by an increase in the hematocrit value and in the blood nonprotein nitrogen level can be demonstrated Often the serum sodium is reduced and the potassium elevated In some cases however hypoglycemia may be encountered and requires emergency treatment After blood is drawn for sodium potassium hematocrit and nonprotein nitrogen determinations a continuous infusion of dextrose and saline should be started at rates from 20 cc down to 2 cc per minute depending on the degree of shock and hemoconcentration Care must be taken not to overload the circulatory system Since a soluble hydrocortisone preparation has become available this preparation can now be given intravenously for a rapid response The effect of hydrocortisone on salt and water metabolism is unpredictable so that desoxycorticosterone intramuscu

ment of Addison s disease may be divided into day to dav management and the management of an intercurrent acute illness which mav cause a so called adrenal crisis

Day to day management —Cortisone 12 5 to 50 mg per day by

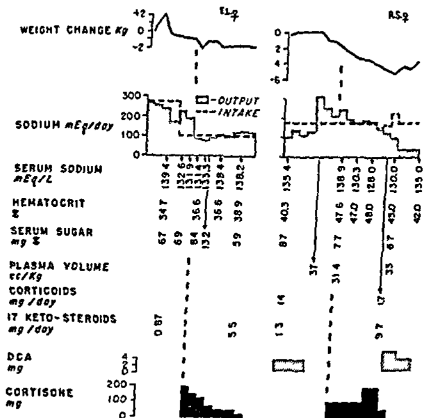


FIG 3 —Variable effect of cortisone on sodium balance in Addison s disease (Courtesy of Dr A I Knowlton and *American Journal of Medicine*)

mouth and hydrocortisone 5 to 40 mg per day by mouth are the 11 oxygenated steroids of choice for the treatment of Addison s disease The most gratifying aspect of cortisone treatment of Addison s disease has been its extraordinary and consistent effect upon appetite and sense of well being Cortisone seems to be effective in protecting patients against the hvpoglycemia which characterized the disease in the past These steroids also effectively protect against the added stress of infections toxins surgery and the like The influence of cortisone

symptoms such as hypertension decreased glucose tolerance and striae

Steroidal studies—Daily variations in the hormonal excretion pattern apparently occur in patients with Cushing's syndrome so that to be of value excretion data should be obtained for several days Furthermore both the 17 ketosteroids and the corticoids may at times be within normal limits

TABLE 3—SYMPTOMS AND SIGNS IN PATIENTS WITH CUSHING'S SYNDROME

SYMPTOMS OR SIGNS	PRESBYTERIAN HOSPITAL SERIES (33 CASES) %	PREVIOUSLY REPORTED (189 CASES) %
Obesity	97	97
Hirsutism	73	69
Hypertension	84	85
Amenorrhea oligomenorrhea impotence in men	86	71
Plethoric appearance	*89*	*50*
Purple striae	60	71
Mental symptoms—major 24% minor 43%	67	31
Poor wound healing or severe infection	42	30
Weakness and backache	83	50
Skin pigmentation acne or other rash	82	26
Purpura or easy bruisability	60	23
Ankle edema	60	28
Headache	58	34
Neurologic symptoms or signs	*39*	*17*
Polydipsia or polyuria	39	25
Virilism	9	5
Exophthalmos	6	8

The 17 ketosteroid excretion values need not be elevated in Cushing's syndrome Forbes and Albright (14) have gathered the data from several large clinics in this country They found that generally speaking the urinary 17 ketosteroid values were only mildly increased in Cushing's syndrome due to adrenal hyperplasia and that in the presence of a benign adrenal adenoma excretion of 17 ketosteroids might even be suppressed There is general agreement however that an adrenal carcinoma may cause a marked elevation of the urinary 17 ketosteroids (Table 4) Nevertheless in 1 of our patients with an adrenal carcinoma the urinary 17 ketosteroids were decreased (6–8 mg/day) until quite late in the disease the increase appeared only after widespread metastases had developed

Androsterone etiocholanolone dehydroisoandrosterone and 11

larly must also be administered Cortisone intramuscularly may be given at the same time Its maximal effect will become manifest 24 hours later *In the presence of shock and a hematocrit value below 50* per cent transfusions can be given These measures should be continued until the patient can take drugs by mouth thereafter treatment gradually goes over into day to day management

HYPERADRENALISM

Hyperadrenalism may result from overactivity in the androgenic sphere and give rise to adrenal virilism or there may be overactivity in the metabolic sphere and result in signs and symptoms of Cushing s syndrome However many cases do not show this distinct dichotomy *presenting instead a mixture of the two This is much more* frequent in Cushing s syndrome than in virilism In pure virilism there are usually no metabolic manifestations

CUSHING S SYNDROME —The classic signs and symptoms of Cushing s syndrome are well known The etiology of this condition has been a subject of some dispute Cushing (7) first postulated that the disease which now bears his name was due to a basophilic adenoma of the anterior lobe of the pituitary Kepler *et al* (33) Albright (1) and others have maintained that the disease is due to overactivity of the adrenal cortex It has now become quite clear that adrenal hyperplasia adrenal adenoma or carcinoma, pituitary adenoma or carcinoma or hypothalamic disease (23) may all cause Cushing s syndrome However no matter what the etiologic background may be the physiologic manifestations are those of adrenal hyperfunction All the signs and symptoms of Cushing s syndrome together with hyalinization of pituitary basophils (Crooke s changes) have been reproduced by the prolonged administration of cortisone (10 62) But in all cases the underlying pathology must be ascertained when the syndrome is diagnosed since the correct therapy depends upon the cause

Signs and symptoms —Plotz Knowlton and Ragan (46) have recently reviewed the cases from the Presbyterian Hospital New York and those combed from the literature The most common signs and symptoms and their incidence are shown in Table 3 It should be borne in mind that not all the symptoms need be present in order to make a diagnosis of Cushing s syndrome and many patients with demonstrated adrenal lesions have not manifested some of the so called classic

sone and tetrahydro-hydrocortisone (two metabolites of the preceding steroids) Only one of our patients with Cushing s syndrome did not excrete increased amounts of urinary corticoids but she did have elevated plasma corticoids (Table 5) In addition Touchstone *et al* (65) and Rosselet Jailer and Lieberman (53) have recently found large amounts of tetrahydro 17 hydroxydesoxycorticosterone in the urine of patients with Cushing s syndrome caused by an adrenal carcinoma This finding may be of great significance because it is known that the precursor of this urinary metabolite compound S (17 hydroxydesoxy corticosterone) has an effect upon salt and water metabolism The

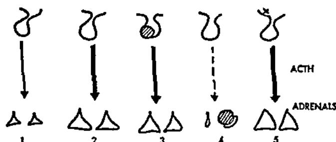


FIG 4 —Possible causes of Cushing s syndrome *1* normal ACTH → adrenal axis *2* excessive production of ACTH *3* basophilic adenoma *4* adrenal tumor *5* hypothalamic involvement.

patients in whom increased amounts of tetrahydro 17 hydroxydesoxy corticosterone were found it should be noted were edamatous at the time the urines were collected

The blood levels of the corticoids are also elevated in Cushing s syndrome Table 5 lists the values found in patients with this syndrome by Wallace and Christy (66)

ETIOLOGY —Figure 4 shows diagrammatically all the possible causes which may give rise to Cushing s syndrome Various tests have been *employed in an attempt to discover* the specific etiology in each case

Roentgenography —Presacral aerography a recently developed method is of great value in demonstrating adrenal tumor Technically roentgenography does not give as satisfactory results in Cushing s syndrome as it does in normal individuals or in virilism

Cortisone test —This method may be of some use in establishing the

EDITORS NOTE —Several cases of Cushing s syndrome caused by thymic tumors have been reported since Leyton first drew attention to this syndrome

TABLE 4 —17 KETOSTEROID EXCRETION IN CUSHING S SYNDROME

	PATIENT	SEX	17 KS MG./DAY
Adenoma	P T	M	14 9 15 6 11 4
	M T	F	20 6 24 2 26 0
	G M	F	2 5 8 2 3 6
Carcinoma	K S	F	18 4 19 1 9 7
	M S	F	51 8 83 0 61.5
	A R	M	35 5 51 6 40 8
	E L	F	51 0 110 0
Hyperplasia	K R	F	17 4 14 4
	F C	F	5 8 2.9 6 3
	A G	F	23 8 15 1 22 9
	H H	F	25 7 19 2 20 2
	C C	F	14 3 9 0
	C P	M	25 0 20 6
	J J	M	13 5 10 2 24 7
	J T	F	29 0 25 4 27 0
	S K	M	9 3 10 0 13 3
	D W	F	9 6 13 5
	C T	M	32 7
	R K	F	10 0

TABLE 5 —PLASMA AND URINARY CORTICOIDS AND URINARY 17 KETOSTEROIDS IN PATIENTS WITH CUSHING S SYNDROME (66)

CASE	ETIOLOGY	PLASMA CORTICOIDS µG /100 ML PLASMA	URINARY CORTICOIDS MG /DAY†	17 KS MG /DAY
1	Adrenal carcinoma	43 0 57 2	13 2 16 9 12 7	52 7 34 6
2	Adrenal hyperplasia	92 0 107 3	47 8 41 5 34 6	47 4 39 0
3	Adrenal adenoma	28 7 37 7	5 9 8 4	14 9 15 6
4	Adrenal hyperplasia	38 4 33 4	7 6 15 5	17 0 21 0
5	Adrenal hyperplasia	36 7	15 5 19 0	25 0 20 6
6	Adrenal hyperplasia	36 5 43 7	3 4 4 6 5 9	5 8 6 3 7 9
7	Adrenal hyperplasia	41 1	19 2 14 3	10 2 9 1

N mal values u in ry c t ds 3 5-9 0 mg /day plasma co t ds 6 0–28 0 µg /100 ml plasma u n y 17 ketosteroids mal 10– 0 mg /d y fem l 6–15 mg

† The urin ry corticoids m y b n mal in some cas of docum nt d Cush ng s yndrome

oxygenated 17 ketosteroids such as 11 ketoetiocholanolone and 11 hydroxyandrosterone are the compounds usually found These steroids as has been shown previously are normally present in the urine

The urinary corticoids as estimated by the Porter Silber technic are almost invariably elevated in Cushings syndrome and excessive amounts of cortisone and hydrocortisone have been isolated from the urine of patients with this syndrome together with tetrahydrocorti

and cortisone administration is continued until it is clear that the patient can maintain his own adrenal secretion. The regimen usually adhered to is shown in Table 6 (30).

In the rare cases in which the pituitary is involved and both adrenals are enlarged, irradiation of the pituitary is beneficial. Surgical removal of basophilic adenomas, which never attain considerable size, is not indicated as a rule. Pituitary irradiation has also been used in the treatment of bilateral adrenal hyperplasia, but the effect is temporary and unpredictable.

Subtotal adrenalectomy.—In the presence of bilateral adrenal hyperplasia, Mayo Clinic investigators (47) have found that subtotal adrenalectomy with the removal of about 90 per cent of the functioning adrenal tissue results in a remission of Cushing's syndrome. Our experience is similar. This is probably true even in those cases in which a basophilic pituitary tumor is present but not demonstrable. Most of the patients require no postoperative replacement therapy with cortisone or DCA. However, some of our patients need small doses of cortisone and DCA for maintenance. The adrenal insufficiency following too drastic removal of the adrenal resembles closely the spontaneously occurring Addison's disease. In such patients the pigmentation characteristic of Addison's disease develops. On the other hand, in about half of the cases, preoperative hypertension persists despite the induced hypoadrenalism which may even require cortisone administration. This may be due to the fact that the hypertension was not related to Cushing's syndrome or that certain irreversible arteriolar changes occurred which were unaffected by the cessation of the hyperadrenal state.

As a rule, no therapy is required when the first adrenal is removed. Before any additional adrenal tissue is removed it is advisable to administer 200 to 300 mg. of cortisone per day for 2 to 3 days postoperatively; it is withdrawn gradually to ascertain whether replacement therapy is needed. Desoxycorticosterone is given on the day of operation and discontinued as soon as the hematocrit, serum sodium, and potassium values become normal. ACTH, of course, is not necessary.

Adrenal Virilism

Virilism may be defined as the masculinization of the female and the attainment of precocious puberty in the male. This clinical state may be caused by a number of endocrine disorders, the most common be

presence or absence of a tumor in Cushings syndrome In most cases of the syndrome due to adrenal hyperplasia administration of cortisone will cause a fall in the urinary 17 ketosteroids when the syndrome is due to adrenal tumor no such fall occurs The test is more reliable in adrenal virilism than in Cushings syndrome (31) it is described in detail in the discussion of the adrenogenital syndrome

Steroidal values—As pointed out earlier, the presence of markedly elevated 17 ketosteroid values may point to the presence of an adrenal

TABLE 6—PRE AND POSTOPERATIVE HORMONE THERAPY WITH REMOVAL OF ADRENAL ADENOMA OR CARCINOMA

Preoperative day 3 ACTH 25 mg q 6 hr i m
2 ACTH 25 mg q 6 hr i m cortisone 100 mg b i d i m
1 ACTH 25 mg q 6 hr i m cortisone 100 mg b i d i m
Day of operation ACTH 25 mg 6 hr i m DCA 5 mg in A M cortisone 100 mg b i d
Neosynephrine or norepinephrine infusions to maintain blood pressure post operatively if necessary
Blood saline etc as needed
Postoperative day 1 As on day of operation
2 If situation is favorable—hematocrit sodium and potassium values normal—DCA omitted and cortisone cut to 150 mg
3 And thereafter Gradual decrease in cortisone and ACTH dosage if hematocrit sodium and potassium values are maintained However ACTH is continued after cortisone has been discontinued

carcinoma It is claimed that with carcinoma elevated values of dehydroisoandrosterone are also encountered In our experience this too has not been a constant feature in Cushings syndrome There is no one steroid found in the urine which is diagnostic of Cushings syndrome

TREATMENT OF ADENOMA OR CARCINOMA—An adrenal tumor calls for surgical removal In preparing the patient for surgery it should be remembered that cortisone inhibits ACTH production Since the corticosteroids produced by the adenoma may have caused atrophy of the contralateral adrenal removal of a tumor may leave the patient without any functioning adrenal tissue at the very time that he has undergone the serious stress of operation The patient should therefore be prepared for operation with this in mind ACTH is administered for 3 or 4 days before the operation to stimulate the contralateral adrenal so that it will respond to the endogenous ACTH which the pituitary will secrete after the tumor is removed Of course cortisone is also given for a few days before and after the operation to prevent a sudden transition from the hyperadrenal to the hypoadrenal state ACTH

virilism certain signs and symptoms of Addison s disease The infants with this condition have great difficulty in retaining sodium and excreting potassium (64 68) In contrast to the true addisonian patient however carbohydrate metabolism is normal although White and Sutton (67) have described one such patient who had episodes of hypoglycemia The former belief that in adrenal virilism the adrenals were secreting excessive amounts of androgen but were producing less salt and water regulating steroids has been shown to be inexact Recently it has been demonstrated that further stimulation of the adrenals with ACTH increases the salt output (26 28 35) We have produced a mild addisonian crisis in one such patient with the serum sodium falling from 134 to 125 mEq in 3 days This occurred during ACTH therapy and despite the fact that the patient was receiving 5 Gm of added salt and 5 mg per day of desoxycorticosterone We surmised that the adrenals in such cases must be secreting a steroid or steroids which cause sodium excretion rather than sodium retention so that an adrenal crisis was produced when the adrenals were further stimulated by exogenous ACTH

In children adrenal virilism is attended by a sudden increase in linear growth and muscular development The bone age usually shows an acceleration A husky voice and acne may develop In the male the penis becomes enlarged and there is growth of pubic and axillary hair the testes however usually remain infantile In the female the size of the clitoris is often markedly increased in addition to the growth of pubic and axillary hair However hirsutism is not a marked symptom in this condition as contrasted to the hirsutism often seen in females past puberty in whom no adrenal lesion is found The complete picture of virilism in the adult woman is characterized by amenorrhea hirsutism voice changes acne atrophy of the breasts enlargement of the clitoris and abnormal muscular development

STEROIDAL FINDINGS —In virilism due to adrenal hyperplasia or carcinoma, the urine contains exceedingly large quantities of steroids The monograph of Dorfman and Ungar (11) lists the various types of urinary steroids found in this condition The urinary 17 ketosteroids are invariably elevated in adrenal hyperplasia and are of great diagnostic aid Table 8 shows the urinary 17 ketosteroid findings in several of the patients studied in this clinic The more commonly found 17 ketosteroids are etiocholanolone androsterone Δ^9 androstenolone (an artefact derived from 11 hydroxyandrosterone) and 11 ketoetiocho

ing an aberration in adrenal function When the underlying cause is an adrenal lesion the disease is called adrenal virilism The clinical manifestations of adrenal virilism depend upon the age at onset and the patient s sex The various manifestations of adrenal virilism and its differentiation from other types of virilism have been adequately reviewed by Wilkins (70) Soffer and associates (60) and Jailer (29)

TABLE 7 — MANIFESTATIONS OF ADRENAL VIRILISM ACCORDING TO TIME OF ONSET

Male		Female
Congenital		
Macrogenitosomia praecox		Pseudohermaphrodite
1 Pure		1 Pure
2 With addisonian like symptoms		2 With addisonian like symptoms
	Hyperplasia > tumor	
Prepuberally		
Macrogenitosomia praecox		Virilism
	Tumor > hyperplasia	
Postpuberally		
(?)		Adrenogenital syndrome
		Cushing s syndrome—some degree of virilism
	Tumor > hyperplasia	

Table 7 summarizes the clinical manifestations of adrenal virilism according to age at onset and sex The congenital form of adrenal virilism is manifest at birth or shortly thereafter In the female various degrees of female pseudohermaphroditism are present in the male the disease may not become manifest for about a year or two The condition is invariably caused by bilateral adrenal hyperplasia The prepuberal type of adrenal virilism occurs at any age between 1 year and puberty the cause in most cases is an adrenal adenoma or carcinoma and in a few there may be adrenal hyperplasia as well The clinical status in the presence of an adrenal carcinoma usually includes some of the elements of Cushing s syndrome—metabolic dysfunctions diabetes hypertension striae the metabolic manifestations are absent if the virilism is caused by an adenoma The disease may have its onset after puberty as well mainly in women and rarely in men Only a few cases of feminization in the male due to adrenal carcinoma have been reported

In a rare variant of adrenal hyperplasia there are in addition to

TABLE 9 —Results of Cortisone Test in Adrenogenital Syndrome

Patient	Age, Yr	Control 17 KS Excretion Mg /Day	Cortisone Dosage (Mg) Route	17 KS Excretion on Cortisone Regimen † Mg /Day
Due to Adrenal Hyperplasia				
		Female Pseudohermaphrodites		
K A	14	51 4	100 i m × 5 d ‡	5 6
R E	11	20 3	100 i m × 4 d	4 6
T K	13	30 8	200 i m × 5 d	13 3
A M	16	79 1	200 i m × 5 d ‡	13 6
J L	15	34 9	50 i m × 4 d	9 6
B L	3	8 96	25 i m × 4 d	2 2
C B	17	28 8	200 i m × 4 d	10 6
F K	8	23 4	75 p o × 6 d	6 1
D P	18	61 1	100 i m × 5 d	20 1
C A	17	63 9	50 p o × 11 d	1 6
C D	½	13 6	50 i m × 4 d	4 7
J B	8	13 5	75 i m t i w × 30 d	2 3
J P	3 wk	9 2	5 p o × 6 d	3 95
S F	3	6 5	25 p o × 5 d	3 0
		Macrogenitosomia Praecox		
Re W	4	16 5	100 i m × 9 d	2 5
Ra W	6	26 3	100 i m × 5 d	5 3
E B	9	34 6	200 p o × 4 d	6.5
A L	8	19 2	25 p o × 10 d	13 2
W H	4	19 4	100 p o × 4 d	2 4
L Y	3	9 5	100 i m × 4 d	3 7
Due to Adrenal Neoplasia				
			Adenoma	
P B ♀	23	56 0	200 i m × 5 d	74 0
A F ♀	4½	14 9	35 i m × 4 d	14 3
			Carcinoma	
A P ♀	13	36 5	100 i m × 5 d	36 2
M C ♀	42	24 0	100 i m × 6 d	20 0

Values r pres nt g f 1 k toster d reti n o e app x m tely a 1 week p od
† V l es p es nt a rag of 17 k toster d e retı n f last 3 d ys f tıs n adm ıst t n
‡ Rec ed hydroc rt o

oxygenated 17 ketosteroids are not particularly elevated nor are the many pregnane derivatives seen

Differentiation between adrenal neoplasia and hyperplasia —As mentioned earlier the steroidal pattern is somewhat different in the presence of an adrenal tumor and the finding of large amounts of dehydroisoandrosterone definitely points to an adrenal tumor A some

lanolone In addition to the C 19 17 ketosteroids many pregnane derivatives are found They are pregnanetriol pregnanediol 11 keto pregnanolone pregnanolone recently Finkelstein von Euw and

TABLE 8 —17 KETOSTEROID VALUES IN PATIENTS WITH ADRENAL VIRILISM

PATIENT	AGE	SEX	17 KS MG /DAY	REMARKS
			Adrenal Hyperplasia	
A R	8 mo	F	11 3	Pseudohermaphrodite
T K	4 yr	F	26 0	Pseudohermaphrodite
	14 yr		34 2	
C R	7 yr	F	42 8	Pseudohermaphrodite
	12 yr		62 4	
B L	15 mo	F	9 0	Pseudohermaphrodite
C D	2½ yr	F	16 5	Pseudohermaphrodite
J L	13 yr	F	46 1	Pseudohermaphrodite
K A	14 yr	F	46 7	Pseudohermaphrodite
R E	10 yr	F	17 2	
R K	8 yr	F	19 8	
B F	4½ yr	"F"	9 8	True hermaphrodite with virilism
E B	5 yr	M	24 8	Macrogenitosomia praecox
	7 yr		28 2	
J T T	6 yr	M	17 4	Macrogenitosomia praecox
W H	3½ yr	M	21 6	Macrogenitosomia praecox
A R	9 yr	M	19 2	Macrogenitosomia praecox
S B	2½ yr	F	5 5	Pseudohermaphrodite with addisonian like symptoms
L Y	15 mo	M	11 1	Virilism with addisonian like symptoms
			Adrenal Adenoma	
F N	7 yr	M	175	Adrenal adenoma
			6	After removal
M H	6 yr	F	189	Adrenal adenoma
			4	After removal
			Adrenal Carcinoma	
K C	42 yr	F	37 8	Mixed syndrome—Cushing s and virilism

Reichstein (13) have isolated pregnanetriol 11 one from the urine in this condition The urinary and plasma corticoids appear not to be elevated

The steroids found in the urine of patients with adrenal virilism due to an adrenal adenoma or carcinoma differ somewhat from those found in adrenal hyperplasia Dehydroisoandrosterone is the steroid often found in highest concentration in the former condition The 11

cortisone over a 4 to 5 day period does not cause a fall in the urinary 17 ketosteroids whereas in the presence of adrenal hyperplasia there is a marked fall Similar results were obtained by the intravenous ad ministration of 100 mg of hydrocortisone over a 4 hour period (Fig 5) The patient with adrenal hyperplasia responded to the infusion with a prompt fall in urinary 17 ketosteroids whereas the patient with virilism due to tumor under identical circumstances showed a rise in the urinary 17 ketosteroids

Previous work had demonstrated that among other physiologic effects cortisone and hydrocortisone inhibit ACTH production and consequently put the adrenal to rest The same mechanism may oper ate in this condition Cortisone inhibits ACTH production and puts *the pathologic adrenal "to rest" at the same time it supplies a more* normal adrenal hormone than is usually secreted

TREATMENT—Adrenal hyperplasia is treated by prolonged admin istration of cortisone or hydrocortisone The dosage varies with the age of the patient The younger children require less cortisone than do the older The best guide to cortisone administration is the mainte nance of urinary 17 ketosteroid values close to those considered nor mal for the age and sex of the individual As little as 50 mg two or three times a week in the age group up to 6 years is sufficient In the 16 to 17 year age group 75 to 100 mg two to three times a week intra muscularly usually suffices Unfortunately cortisone by mouth is not as effective in maintaining a steady reduced level of urinary 17 keto steroids As a result of our experience we prefer intramuscular admin istration It should be borne in mind that the aim of cortisone therapy is to inhibit ACTH production and not to attain the "hyperadrenal state" such as is necessary in the treatment of rheumatoid arthritis or the allied diseases Furthermore the usual toxic effects of cortisone overdosage though rare may occur In addition the adrenal may be put at rest" to such a degree by prolonged administration of cortisone that the equivalent of adrenal insufficiency may appear when the pa tient is exposed to stress This is particularly apt to happen when the cortisone dosage is reduced

Surgical extirpation is the only treatment available for virilism due to an adrenal adenoma In contrast to the usual findings in Cushing s syndrome in adrenal virilism the contralateral adrenal is not atro phied These patients are therefore good operative risks and need no preoperative preparation with hormonal replacement therapy

what simplified but not rigorously specific test for dehydroisoandrosterone has been proposed by Allen and co workers (2) Since the treatment differs radically with the cause certainty whether a tumor is present or not is essential

The simple technic of presacral aerography introduced in the past few years has markedly simplified the roentgenographic examination of the adrenal area In most cases an adrenal tumor can be diagnosed by means of this test

CORTISONE TEST—Wilkins *et al* (69) Bartter, Albright, *et al* (4)

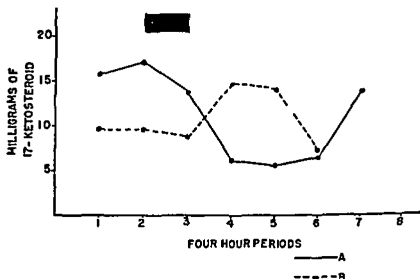


FIG 5—Results of intravenous hydrocortisone test *A* in bilateral adrenal hyperplasia with virilism *B* in adrenal adenoma with virilism (Courtesy of *American Journal of Medicine*)

and Jailer Louchart and Cahill (27) have demonstrated that administration of cortisone to patients with adrenal hyperplasia causes the urinary 17 ketosteroids to decline from the characteristically elevated levels to values approximately normal for the age and sex of the patient Hydrocortisone was subsequently found to be as effective as cortisone Cortisone 50 and 200 mg a day intramuscularly according to age and size of the patient, may be administered for 5 days or hydrocortisone intravenously 100 mg over a 4 hour period Table 9 shows the results of the intramuscular test As can be seen in the presence of an adrenal adenoma or carcinoma the administration of

hydroxylation of progesterone to hydrocortisone is defective and certain of the precursors—17 hydroxyprogesterone and 21 desoxyhydrocortisone—are secreted instead (Fig 6) Some of the metabolites of these steroids are androgenic and can amply account for the virilism

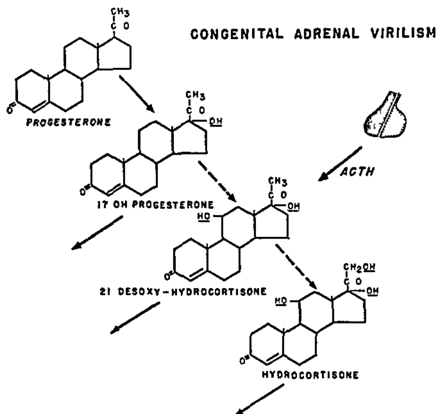


Fig 6—Postulated enzymic block in congenital adrenal virilism

so characteristic of this condition Since as a result of this enzymic block the amounts of hydroxycortisone would be inadequate the pituitary would begin to secrete an excess of ACTH in order to produce sufficient hydrocortisone for hemostasis Indeed Sydnor and collaborators (63) found excessive amounts of circulating ACTH in the plasma of patients with congenital adrenal hyperplasia This could also account for the adrenal hyperplasia

The administration of cortisone results in the inhibition of ACTH

CONGENITAL ADRENAL HYPERPLASIA AS INBORN ERROR OF METABOLISM —Apparently, congenital adrenal hyperplasia must be considered an inborn error of metabolism The disease is present at birth and it often occurs in siblings In our own series of 25 patients there are 5 families which have more than one member with congenital adrenal hyperplasia and virilism Patients with congenital adrenal hyperplasia respond somewhat differently from normal individuals to ACTH administration they manifest *no* increase in urinary or plasma corticoids (28 32 35) *no* sodium retention (4 28) and *no* fall in circulating eosinophils (4 28) On the other hand a rise in the already elevated values of the 17 ketosteroids and in "pregnanediol" values has been demonstrated This seems to suggest that after stimulation by exogenous ACTH the adrenals of such individuals secrete hydrocortisone with difficulty but can very readily secrete a steroid or steroids which are precursors of urinary 17 ketosteroids and pregnanediol It will be recalled that many investigators have shown that adrenal tissue is capable of hydroxylating progesterone at the C 11 C 17 and C 21 position with the resultant formation of hydrocortisone

17 Hydroxyprogesterone has been isolated from adrenal tissue by Pfiffner and North (45) who have claimed that it is also androgenic In man 17 hydroxyprogesterone is metabolized to the 17 ketosteroids—androsterone and etiocholanolone—and the pregnane derivatives pregnanolone 17 OH pregnanolone pregnanetriol and pregnanediol These of course are steroids which are usually found in the urine of patients with congenital adrenal hyperplasia The precursor itself cannot possibly account for the high values of 11 oxygenated steroids in the urine of patients with adrenal hyperplasia Consequently it was also postulated that if 17 hydroxyprogesterone were hydroxylated at the C 11 position and this was secreted by the adrenal it could account for the 11 oxygenated steroids that are found in the urine of patients with congenital adrenal hyperplasia 21 Desoxyhydrocortisone has been administered to 2 patients with low initial 17 ketosteroid values and the following steroids have been isolated from the urine Δ^9 androstenolone Δ^9 etiocholanolone (these are artefacts derived from 11 hydroxy compounds) 11 ketopregnanolone and although not identified possibly pregnanetriol 11 one The metabolites of 17 hydroxyprogesterone and 21 desoxyhydrocortisone could therefore account for the individual steroids found in the urine in congenital adrenal hyperplasia From this the occurrence of a metabolic defect has been postulated in which the normal

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production and consequently puts a diseased adrenal "to rest" and at the same time supplies a more normal hormone This of course results in a decrease in the urinary 17 ketosteroids and eliminates from the urine the steroids which are characteristic of adrenal virilism

ADRENAL ADENOMA —The metabolic aberrations responsible for adrenal virilism due to an adrenal adenoma or carcinoma differ from those of congenital adrenal hyperplasia This is suggested by the fact that the predominant steroid in the former condition is dehydroisoandrosterone The origin of this steroid in adrenal tissue is obscure Lieberman and Teich (38) suggest that 17 hydroxypregnenolone may be the precursor of urinary dehydroisoandrosterone It will be recalled that an enzyme system present in the adrenal gland can convert a Δ^5 steroid to a Δ^4 it is entirely possible that the presence of an adrenal tumor interferes with this conversion As a consequence the adrenal will secrete a cholesterol like steroid a pregnenolone which can be metabolized to dehydroisoandrosterone

The current descriptions of the clinical disorders caused by overactivity of adrenocortical tissue show how developments in the field of steroidogenesis and their application to clinical conditions have made possible great advances in this field in the last few years The ultimate aim of investigators in this field is to be able to explain the clinical abnormalities in terms of known biochemical alterations in steroid synthesis and steroid action

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Diseases of the Pericardium

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DIAGNOSIS

Critical Evaluation of Signs and Symptoms

Because opinion concerning the significance of various symptoms and signs of pericardial disease is not uniform a brief evaluation of selected manifestations is not considered too elementary for a review of this type

(1) Pain —Early views on the nature of pericardial pain were reviewed in a classic monograph by Capps and Coleman (28) and observations on patients undergoing pericardiocentesis were described Discomfort due to pericardial involvement may vary from a severe sharp stabbing pain to a dull ache primarily localized to the precordial or substernal area It may also involve the epigastrium left side of the neck and shoulder and left subscapular area and may be aggravated by cough ing, swallowing, precordial pressure movement of the thorax the re cumbent position or breathing The distribution of sensory branches of the phrenic nerve to the lower portion of the pericardium (as well as to the diaphragmatic pleura) provides the basis for shoulder or trapezius pain in pericarditis

Friction rub —The friction sound of pericarditis may be only systolic in time especially in the stages when the pericarditis is developing or resolving When intense it may display a quadruple nature "choo-choo-choo-choo" in each cardiac cycle More often, three components at the most are present systolic, protodiastolic, and presystolic (38) (see Plate 4, *B*) Pericardial frictions can be confused with to-and fro

double aortic murmurs or vice versa Characteristically pericardial frictions are changeable and evanescent, seem superficial and have no uniform localization They are best heard with the patient in upright position and with increased pressure of the bell or the diaphragm of the stethoscope against the chest wall The area of maximal intensity varies with time and with change in position of the patient The presence of pneumohydropericardium most commonly iatrogenic adds the millwheel sound *(bruit de moulin)* and endows the friction sounds with a metallic tinkling quality the heart sounds having at times an amphoric quality

SOME MANIFESTATIONS OF EFFUSION —As pointed out by Auenbrugger (5) a sharp change in the percussion note from resonant to dull or flat in outlining the cariovascular silhouette is characteristic The apical impulse may be visible even after the accumulation of a sizable pericardial effusion (1 000 cc or more) In such instances the apical impulse is likely to be well within the left border of dullness (or flatness) The persistence of a friction rub in the face of considerable effusion is another seeming inconsistency

An area of dullness with bronchial breathing and bronchophony or egophony located posteriorly at the left lung base was described by Pins of Vienna in 1889 (128) and Ewart of England in 1896 (52) In our experience it is not encountered more often in association with the pericarditis of rheumatic fever (164) than with other varieties

Patients with pericardial effusion are often dyspneic only in the recumbent position although they seldom have a significant degree of pulmonary congestion The mechanism of this orthopnea is not entirely clear In contrast to the orthopnea in heart failure due to other causes relief is often attained not merely by elevating the head and shoulders but by leaning forward In severe cases the patient will elect the knee chest position *(signe de la priere mahometane)* The choice of position may be dictated by the relief of pain as much as of dyspnea

SOME MANIFESTATIONS OF CARDIAC TAMPONADE —Although commonly present the hepatojugular reflex—bulging of the neck veins and rise in venous pressure in the neck and arm veins when pressure is applied over the liver and the closely related inspiratory filling of the neck veins (73) are not specific indications of inflow stasis due to pericardial disease as opposed to other types of heart failure The reflux of blood causing the hepatojugular reflex is explained by the fact that in constrictive pericarditis the output of the right ventricle is fixed and is

A CLASSIFICATION OF DISEASES OF THE PERICARDIUM

I Acute (and subacute) disorders
  A Acute nonspecific (benign idiopathic) pericarditis
  B Pericarditis due to living agents
    1 Tuberculous
    2 Purulent (pyogenic)
      a) Pneumococcal
      b) Streptococcal
      c) Staphylococcal
      d) Neisserian
      e) Friedlander
      f) Tularemic (142 102)
      g) Meningococcal (111 99 86)
      h) Secondary to hepatic or subphrenic abscess (113 139 111 158)
      i) Hemophilus influenzae (148)
    3 Protozoal
      a) Echinococcal
      b) Amebic (28 43)
      c) Necator americanus (144)
    4 Mycotic
      a) Actinomycosis (168)
      b) Coccidioidomycosis
    5 Viral (?) e g mumps (?) lymphopathia venereum (132) infectious mononucleosis (135 115)
  C Connective tissue disorders and allergic diseases
    1 Rheumatic fever
    2 Systemic lupus erythematosus
    3 Allergic granulomatosis
    4 Rheumatoid arthritis
    5 Serum sickness
  D Chemical or metabolic
    1 Uremia
    2 Diabetic acidosis
    3 Addison s disease
    4 Myxedema
  E Neoplastic
    1 Primary (169 170)
    2 Metastatic
    3 Lymphomatous e g Hodgkin s disease (57 58 91)
    4 Leukemic (11)
  F Pericarditis secondary to abnormalities of heart and great vessels
    1 With myocardial infarction
    2 With coronary embolism
    3 With dissecting aneurysm of the great vessels
    4 With bacterial endocarditis
  G Pericarditis with a physical basis
    1 Trauma
    2 X ray
II Chronic disorders of pericardium
  A Chronic constrictive pericarditis
  B Chronic mediastinopericarditis
  C Chronic pericardial effusion (55 93)
    1 Myxedema (61)
    2 Cholesterol pericarditis
    3 Chylopericardium
    4 Anemia (136)
    5 ? Trauma (160)
    6 Chronic idiopathic pericardial effusion
  D Pericardial cyst and diverticulum
  E Congenital absence of pericardium (137)

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therefore unable to cope with the additional blood presented to it when pressure is applied to the liver

The term "pulsus paradoxus" was applied by Kussmaul (87) to the phenomenon of a weak or imperceptible pulse on inspiration although the heart sounds continued with unaltered intensity and rhythm The phenomenon does not represent a paradox as slight drops in systolic arterial blood pressure normally occur with inspiration Lack of specificity makes the sign of doubtful usefulness It occurs in various respiratory disorders especially bronchial stenosis and other types of air way obstruction including asthma The common denominator in the latter group is an increase in the range of variation of intrathoracic pressure with respiration that is an excessive increase of negative pressure during the inspiratory phase It also occurs in patients with dilated and atonic hearts Although some drop in systolic pressure usually occurs with inspiration in normal individuals this is rarely more than 10 mm Hg with quiet breathing this value can be taken as a level of significance for true pulsus paradoxus

Differentiation of the pulsus paradoxus of pericardial origin from that of respiratory origin may be aided by observation of the neck veins in air way obstruction the neck veins are apt to show collapse during the exaggerated negative pressure phase of inspiration whereas in cardiac tamponade inspiratory filling of the neck veins occurs Because of the venous engorgement already present inspiratory filling can be better appreciated during determination of venous pressure especially in the jugular veins) than by direct inspection

The right upper quadrant pain of pericardial effusion and of constrictive pericarditis is probably due largely to stretching of the liver capsule but at times to perihepatitis ("sugar coated liver" *Zuckergussleber)* The latter represents the deposition of fibrin on the surface of the liver as a result of elevated hepatic venous pressure It has been produced in dogs with chronic constrictive pericarditis induced by wrapping the heart in scar stimulating polyethylene (108) Occasionally the enlarged liver in constrictive pericarditis crunches on pressure like dry snow and there is a conspicuous friction rub Onset of right upper quadrant pain may be abrupt and the initial complaint in some cases of constrictive pericarditis

SYSTOLIC CLICKS —The synonymous term "systolic gallop" is best avoided Systolic clicks (Plate 1 *A)* are a rather frequent auscultatory finding and are included here because there is evidence that the most

common cause is pericardial adhesion or pericardial roughening from past pericardial involvement The sign s lack of clinical importance deserves emphasis The evidence for its pericardial origin consists of autopsy correlations (56) and fluoroscopic observations of systolic tugging of external adhesions on the diaphragm synchronous with the adventitious sounds (97) Similar sounds may occur from other causes dilated pulmonary artery or aorta (early systolic click) ventricular aneurysm mediastinal emphysema movement of costochrondral or chondrosternal joints and others

Sometimes the systolic click introduces a short and circumscribed midsystolic murmur This type of murmur (Plate 1 *B*) like the click is of extracardiac origin and is benign

Ancillary Diagnostic Measures

Pericardiocentesis is frequently necessary to establish the diagnosis of pericardial effusion The principal routes employed are the subxiphoid apparently first introduced by Marfan, and the apical Some prefer the apical route because the thick walled ventricle may act as a better landmark when the effusion is hemorrhagic Parasternal tap entails risk of puncturing internal mammary or possibly coronary vessels

Distinct hazards are associated with pericardial tap Occasionally collapse comparable to "pleural shock occurs and in 2 cases sudden death followed introduction of the needle One patient had uremic pericarditis and the other systemic lupus erythematosus It is advisable to administer atropine together with an agent of the morphine group in preparation for pericardial paracentesis

The character of the pericardial fluid will usually permit identification of purulent (pyogenic) pericarditis and the more bizarre varieties such as chylopericardium and cholesterol pericarditis L E cells have been described in pericardial fluid (36 144) A hemorrhagic effusion may occur with tumor rheumatic fever tuberculosis and after trauma and myocardial infarction When anticoagulants are given for any reason the hemorrhagic nature of the effusion may be exaggerated or an effusion not ordinarily hemorrhagic may become bloody The pericardial effusion of uremia is often bloody as a result of the hemorrhagic tendency in this condition In chronic pericardial effusion just as in chronic ascites and chronic pleural effusion proliferation and

desquamation of mesothelial cells occurs The presence of these cells in the fluid sediment may lead to an erroneous diagnosis of metastatic neoplasm

Markedly bloody pericardial fluid raises the question whether the blood was withdrawn from the heart itself The first and easiest differentiating test is a comparison of the hematocrit value and white blood cell count of the fluid with that of venous blood In addition bloody pericardial fluid is not likely to coagulate after withdrawal whereas venous blood does As a further aid in resolving this problem the color of the serum drawn from an arm vein 2 or 3 minutes after injection of Evans blue dye (T 1824) may be observed Injection of agents used in determining circulation time e g calcium gluconate may also be helpful (116)

Instillation of air into the pericardium after withdrawal of fluid may provide significant information (*1*) the heart size can be evaluated (*2*) thickening of the parietal pericardium can be demonstrated and the presence and extent of adhesions and loculations evaluated (*3*) artificial pneumopericardium may serve a useful therapeutic function and help to prevent the subsequent development of constricting pericardial symphysis The procedure also clearly demonstrates how high the pericardial reflections extend on the great vessels (Plate 2) Once this is seen it is no longer difficult to understand why the aorta ruptures so commonly into the pericardial sac why pericardial cysts may be located rather high in the mediastinum and why the pericardium is prone to infection by extension from infected mediastinal lymph nodes

Differentiation of pericardial effusion from myocardial disease with cardiac dilatation presents one of the most difficult problems In both there is a large cardiac silhouette with diminished pulsations and both may be associated with a small pulse pressure pulsus paradoxus gallop rhythm and faint heart sounds Sometimes a slight systolic heave of the left midprecordial area may indicate that the abnormality is myocardial rather than pericardial A localized impulse well inside the left border of pericardial dullness is evidence in favor of pericardial effusion but it can be misleading In cases of pericardial effusion the circulation time tends to be only slightly prolonged or not prolonged in proportion to the degree of venous hypertension (10) Angiocardiography has at times been used (92 163) as an aid in differentiation (Plate 3) in pericardial effusion an abnormally great distance between the dye in the right atrium and the right lung field

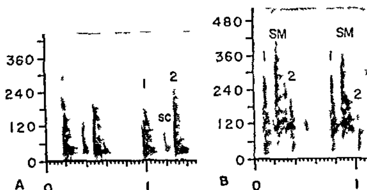


PLATE 1 —Spectral phonocardiograms showing sounds believed to be due to pericardial adhesion and/or roughening *A* midsystolic click *(SC)* *B* circumscribed midsystolic murmur *(SM)* introduced by a systolic click (Spectral phonocardiography displays (109) three dimensions of sounds time [abscissa] in seconds frequency spectrum [ordinate] in cps and intensity [density or blackness] See Fig 5 for other examples) In both instances 1 and 2 refer to the first and second heart sounds respectively



PLATE 2 —Demonstration of the extent of the reflections of the pericardium over the great vessels Note that the pericardial sac extends *to the level of the* aortic arch as seen in the posteroanterior projection Artificial pneumopericardium was performed in connection with investigation of the patient's pericardial effusion probably tuberculous in etiology The patient also has advanced pulmonary silicosis with emphysema



PLATE 3.—*A*, chest x ray and *B*, angiocardiogram of a patient with persisting enlargement of the cardiovascular silhouette several months after stab wound of the heart. Pericardial puncture had been unproductive on several occasions and at several sites. An acute right cardiophrenic angle is displayed in *A*. The angiocardiogram (*B*) leaves no doubt of presence of pericardial thickening. Note the increased distance between the dye filled left atrium and the right lung field.

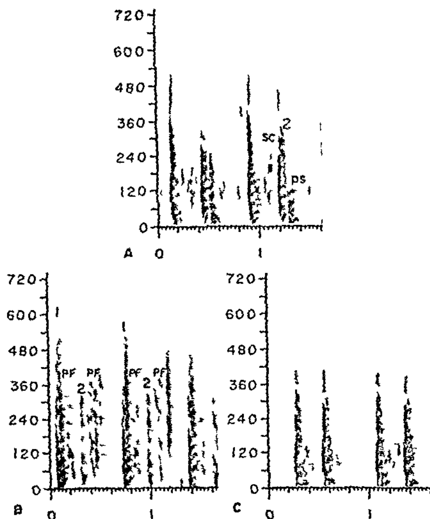


PLATE 4.—The heart sounds in calcific constrictive pericarditis displayed in spectral phonocardiograms recorded before, soon after, and late after pericardectomy. *A*, preoperative. Note the systolic clicks (*SC*) and the protodiastolic sound (*PS*). *B*, early postoperative. Pericardial friction rub (*PF*) mainly systolic and early diastolic in time is demonstrated. *C*, late postoperative. Neither systolic click nor the protodiastolic sound is recorded with certainty.

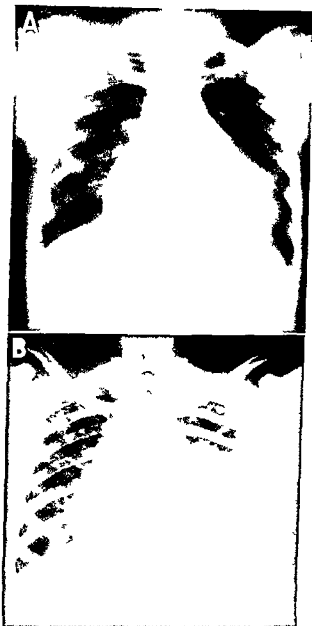


PLATE 5.—Demonstration of the evolution of constrictive pericarditis. The patient was asymptomatic when the miniature chest film *(A)* was taken. Pericardial effusion is clearly present. Two years later, when classic signs of constrictive pericarditis had developed, the heart *(B)* had a triangular shape. There are dilatation of the superior vena cava and pleural effusion on the left.

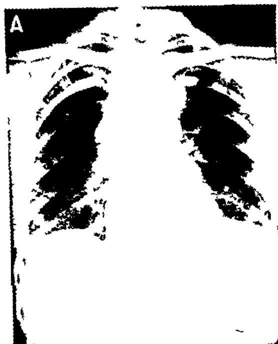




Plate 6.—The patient whose chest x ray is shown in *A* had venous hypertension of both caval systems. Constrictive pericarditis was prominent in the differential diagnosis. Autopsy revealed a malignant thymoma which had invaded the right atrium with blockade of the tricuspid orifice (*B*).



PLATE 7.—*A* one film from a laminagraphic series performed in a case of pericardial cyst located anteriorly in the left cardiophrenic angle Laminagraphy assists in differentiation from ventricular aneurysm *B* appearance of the cyst filled with crystal clear fluid as seen on exposure at thoracotomy *C* after removal from the thorax

should be demonstrable On cardiac catheterization the relation of the catheter to the right lung field when the catheter is resting against the atrial wall will provide the same information (166)

Many roentgenographic signs of effusion have been described These are well summarized by the following statement "None of the many signs suggested in this connection is more than partly successful some are based on a misconception of x ray physics while others ig nore the principles of hydraulics" (47). It has been pointed out that effusions tend to produce an acute right cardiophrenic angle, whereas right ventricular enlargement usually produces an obtuse one (91)

Enlargement of the thymus may result in a roentgenographic ap pearance closely simulating pericardial effusion (12) Study of oblique and lateral projections will help resolve the problem Thymic tumors too are at times difficult to differentiate from pericardial cysts

The T waves of the electrocardiogram are almost invariably altered in patients with well developed constrictive pericarditis The electro cardiographic changes of acute pericarditis can closely simulate those of myocardial infarction The presence of abnormal Q waves and of *reciprocal changes in the ST segments and T waves points to myo*cardial infarction rather than pericarditis However in localized peri carditis such reciprocal changes may occur (22) The S T segments in pericarditis unlike those of myocardial infarction tend to return to the isoelectric line before the T wave becomes inverted (121)

PERICARDITIS

Acute Nonspecific (Benign Idiopathic) Pericarditis

Generally the patient first has an upper respiratory syndrome (120) The pericarditis is ushered in by severe substernal pain aggravated with each heart beat with respiration with movement or turning of the chest, with swallowing and with pressure on the epigastrium or precordium Fever and a polymorphonuclear leukocytosis are usual and are characteristically present when the patient is first seen be cause of the chest pain—a feature which may assist in differentiating this disease from myocardial infarction Effusions may occur but are rarely profuse enough to necessitate pericardial paracentesis for relief of tamponade The course is usually that of a benign and self limited disease Several deaths have been reported, however (103 129) in most instances the patient was thought to have had a myocardial in

farction was treated with anticoagulants and died of tamponade by a hemorrhagic effusion The fluid may be bloody even when anticoagulants are not administered Recurrences sometimes several over a period of years do occur (132) Inconclusive evidence consisting largely of the persistence of electrocardiographic changes and of such symptoms as dyspnea and substernal pain, seems to indicate that myocardial involvement may accompany benign idiopathic pericarditis (63) The occurrence of paroxysmal ventricular tachycardia with benign pericarditis may be evidence of associated myocarditis Certain cases in this group may etiologically be similar to cases of acute idiopathic myocarditis Associated pneumonitis with the characteristics of primary atypical pneumonia have been observed and in 1 of our cases a significant titer of cold hemagglutinins developed "Dramatic response to aureomycin and/or terramycin" has been reported (140 156) There is no evidence that these measures shorten the time required for heart size sedimentation rate and electrocardiogram to return to normal ACTH has also been used (86) but it is unlikely that the basic disease is affected and a risk is entailed if the patient proves to have tuberculous pericarditis

It is likely that in our present state of ignorance benign idiopathic pericarditis should be considered a syndrome not an etiologic entity The situation may be comparable to benign lymphocytic meningitis a syndrome for which more and more separate etiologies are being identified Although rheumatic fever can certainly reproduce this syndrome precisely (44a) to attribute all cases to it seems unwarranted Lupus erythematosus must be kept in mind in such cases Tuberculosis in its mildest form seems to be capable of producing the syndrome (see below) Of the other bacterial pericarditides tularemic pericarditis is perhaps most likely to result in this syndrome When there is associated pneumonitis the psittacosis group of viruses should be kept in mind and investigated by appropriate means

PURULENT (PYOGENIC) PERICARDITIS

The incidence of purulent pericarditis has declined sharply with the advent of specific measures for the treatment of antecedent infections Occasionally cases of pneumococcal pericarditis are still encountered and cardiac surgery is sometimes complicated by infection of the pericardium

Formerly pericardiotomy was indicated as soon as the diagnosis was established and in fact was the only definitive measure available Now in the era of antibiotics one is tempted in cases due to organ isms sensitive to antibacterial agents (pneumococcus streptococcus etc.) to try treatment with repeated pericardiocentesis and large doses of antibiotics The advisability of pericardiotomy in all cases due to relatively insensitive organisms, such as staphylococcus is un questioned Furthermore the opinion that all cases even those due to organisms sensitive to antibiotics should be subjected to pericar diotomy as soon as purulent pericarditis is diagnosed rests on a sound basis

It seems probable that the antibiotics pass into the pericardium in efficiently (45 154) Both the needle and the antibiotic are unlikely to reach the core of the exudate when it is thick and multiloculated Adequate drainage of the pericardium and prevention of recurrent car diac tamponade is assured by pericardiostomy a comparatively be nign procedure Large doses of appropriate antibiotics are indicated as well

Enzymes such as streptokinase and streptodornase have no role in the treatment of this disorder Circulatory collapse has followed their use (31)

The following 2 cases instances of pneumococcal pericarditis illus trate these points of management In both pulmonary involvement was inconspicuous in the early stages of the illness and it was symp toms of pericardial involvement which brought the patient to medical attention

CASE 1 —J G a 35 year old Negro laborer and chronic alcoholic had fallen into icy water 2 weeks before admission He was admitted because of abrupt onset of sharp substernal pains 3 days previously The pain radiated to the left side of the neck and left shoulder and was accompanied by dyspnea and cough which became productive of mucopurulent sputum

On admission the temperature was 101 6 F Blood pressure was 135/70 mm Hg with 20 mm of pulsus paradoxus Percussion revealed the cardiac outline to be greatly increased There was no visible or palpable apical im pulse The heart sounds were faint, and pericardial friction rub was present A few crepitant râles were heard over the right lower lobe but there were no signs of consolidation

The white cell count was 12 200 The pericardial fluid was cloudy and yellow and clotted quickly Pneumococci were cultured from the sputum and demonstrated on stain of the pericardial fluid Failure of the visualized pneumococci to grow may have been the result of earlier penicillin therapy

The electrocardiographic changes were compatible with acute pericarditis Roentgenography showed a huge cardiovascular silhouette but no evidence of pneumonitis

The patient was treated with 6 000 000 units of penicillin and 2 Gm of erythromycin daily Pericardial tap with removal of 300 cc of fluid was followed the next day by signs of severe cardiac tamponade an emergency pericardial paracentesis was performed and 750 cc of fluid removed On the third hospital day signs of consolidation in the left lower lobe appeared Since signs of tamponade again appeared pericardiotomy and open drainage were performed The course thereafter was entirely satisfactory and the patient was discharged well on the sixtieth hospital day

Case 2—L Mck a 72 year old Negro woman complained of vague aching substernal pain the day before admission which subsequently radiated to the neck midback and epigastrium The pain was relieved by leaning forward and aggravated by the recumbent posture

The temperature on admission was 104 F A few moist râles were heard at the right lung base The cardiovascular silhouette was enlarged to the right and left Marked venous engorgement and pulsus paradoxus to the point of obliteration of the pulse in inspiration developed within a few hours of admission After 24 hours signs of consolidation in the right lower lobe developed

The white cell count was only 8 550 rising later to a maximum of 32,000 Type XII pneumococcus was recovered from the blood and pericardial fluid Later pleurisy developed with effusion on the right side pneumococci were identified in the fluid

Treatment consisted of 12 000 000 units of penicillin intramuscularly each day About 24 hours after admission pericardiostomy was performed because of the patient s critical condition and because four pericardiocenteses had been necessary to relieve symptoms of tamponade Recovery was dramatic in view of the patient s advanced age and the existence of bacteremia empyema and pneumonia in addition to pericarditis Fourteen therapeutic thoracenteses were performed The patient remains well

Acute and Subacute Tuberculous Pericarditis

There can be no doubt that streptomycin and the more recently introduced chemotherapeutic agents have greatly increased the rate of cure" in tuberculous pericarditis (30 53) The fatality rate has probably been reduced from about 90 to 95 per cent to 40 to 45 per cent or lower (145) The most effective regimen is not yet established This is not surprising in view of the relatively small number of cases Carroll (30) advises treatment for not less than 6 months

Holman and Willett (75) have advised pericardectomy early in the course of acute or subacute tuberculous pericarditis to prevent the subsequent development of constrictive pericarditis Patients fre-

quently show signs of inflow stasis for an appreciable length of time yet subsequently recover completely How is one to single out those cases which will go on to constriction?

Tuberculous pericarditis rather frequently simulates other forms of heart disease particularly rheumatic and arteriosclerotic The signs of infection may be unimpressive The "gallop rhythm" which is sometimes present may be interpreted as an index of myocardial disease or may even be mistaken for a diastolic murmur Atrial dysrhythmias especially atrial fibrillation which are common in tuberculous pericarditis may be misconstrued as indicating myocardial or valvular disease

Tuberculous pericarditis can present a wide range of clinical severity The patients may be virtually asymptomatic (see Plate 5 A) during the stage of pericardial effusion reporting to a physician for the first time only much later with manifestations of constrictive pericarditis The symptoms in other cases may be mild self limited and recurrent, suggesting benign idiopathic pericarditis Many cases are probably due more to reaction of the pericardial sac to the discharge into it of nonviable tuberculous material from "pericardial" lymph nodes of the mediastinum than to actual infection by the tubercle bacillus Statistics of tuberculous pericarditis such as those cited earlier must be interpreted in this light The patients included in such a series are those who were sufficiently ill to seek medical attention and those in whom at least a strong presumptive diagnosis of tuberculosis can be made

Pericarditis of Systemic Lupus Erythematosus

Pericardial involvement is present at some time during the course of this disease in over 50 per cent of the cases Over a period of years there may be recurrent bouts of pericardial pain often with a friction rub Small effusions may also develop from time to time Rarely are the effusions large although occasionally tamponade may develop and render paracentesis necessary (In one of our cases 2 500 cc of fluid was removed in a single week) Myocardial involvement is also common and during a given period of active disease it may be difficult to determine how much of the cardiac dysfunction results from pericardial and how much from myocardial disease No instance of constrictive pericarditis has been encountered The character of the fluid is not diagnostic L E cells have been discovered in the pericar

dial fluid in 1 reported case (144) and in 1 of our cases A prerequisite for their development in various body fluids such as cerebrospinal fluid, pleural fluid urine and blister fluid is the exudation of a sufficient quantity of the plasma factor" an abnormal gamma globulin It is probable that some rare cases of chronic idiopathic pericardial effusion may, in fact be due to systemic lupus erythematosus without other conspicuous clinical manifestations

The relationship of "spontaneous systemic lupus and the rheumatic syndrome sometimes with demonstrable L E cells which occurs with administration of 1 hydrazinophthalazine hydrochloride (Apresoline hydrochloride) is unclear A patient of ours under treatment with this agent for 2½ years became acutely ill with manifestations of pericarditis and fever L E cells were demonstrated in the blood Upon withdrawal of the hypotensive agent the illness subsided spontaneously As in most of the other patients in whom this syndrome developed, it was difficult to evaluate a history of previous mild manifestations which could well have been early and chronic symptoms of systemic lupus

Chronic Constrictive Pericarditis

Recent investigations of the pathophysiology of constrictive pericarditis will be discussed first *for they explain the physical signs and symptoms*

Physiologic studies —Among the more significant of the studies are the following

1 Correlative studies of recordings of intracardiac pressure curves (from the right ventricle and right atrium) phonocardiograms recordings of ventricular border movement by kymography and ballistocardiograms have shed light on the basis of certain physical findings and provided corroborative diagnostic tests

2 Studies of the circulation in animals with induced pericardial constriction and in man with the analogous condition have elucidated the fundamental physiologic defect in this disorder

3 Studies of pulsus paradoxus have sought the basis of this sign which is physiologically fascinating but of relatively limited diagnostic value

The correlations worked out among the four parameters of cardiac function are shown in Figure 1 First to be considered is the "flat top and V" curve of ventricular border movement as demonstrated by

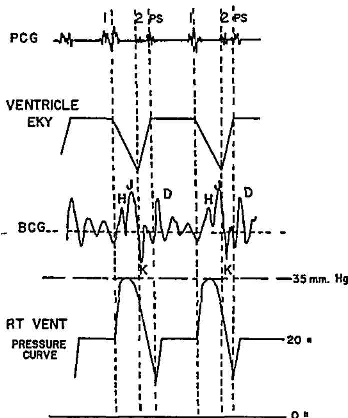


FIG 1—Chart illustrating the correlation of four early diastolic phenomena in constrictive pericarditis There are from above down the adventitious protodiastolic sound *(PS)* of the phonocardiogram *(PCG)* the "flat top and V" pattern of ventricular border movement as displayed by the electrokymogram *(EKY)* the diastolic excursions *(D)* in the ballistocardiogram *(BCG)* and the early diastolic dip of the right ventricular pressure curve

electrokymography or by roentgen kymography (105) It is probable that in constrictive pericarditis the curve of border movement parallels closely the ventricular volume curve It differs from the relatively complex normal curve in the following respects *(1)* Indications of isometric relaxation and isometric contraction are lost *(2)* Ventricular filling becomes very rapid more rapid indeed than systolic ejection, as indicated by the fact that the filling limb of the "V" is steeper than the systolic ejection limb *(3)* Ventricular filling stops abruptly early in diastole and remains at a standstill for the remainder of diastole the latter is an expression of the impediment to diastolic filling of the ventricle The "diastolic heart beat" is a direct translation of this "flat top and V" pattern of ventricular border movement to the anterior chest wall Examination of the electrokymographic pattern makes it clear why tachycardia with abbreviation of diastole will *increase* cardiac output whereas the converse is likely to occur in mitral stenosis because of slow ventricular filling

The adventitious protodiastolic sound of constrictive pericarditis occurs toward the end of the rapid filling phase and at the time of the abrupt halt in ventricular filling when the ventricle is filled to capacity The sound is most probably generated by the rush of blood at this time (due to elevated venous pressure) and by the water hammer effect of the abrupt halt in filling Recent observations suggest that it is not limited to constrictive pericarditis but occurs also with pericardial effusion (74) Phonocardiographically it is distinct from a third sound gallop because of its occurrence earlier in diastole i e closer to the second sound (Plate 4 A)

The ballistocardiogram especially that recorded in the side to side direction shows ballistic excursions in diastole corresponding closely in time to the water hammer point in the recording of border movement In the lateral ballistocardiogram these excursions in diastole are often of such amplitude as to dominate the entire recording (142)

The right ventricular pressure curve, as recorded by cardiac catheterization shows a characteristic diastolic pattern in constrictive pericarditis (67 108 168) This pattern consists of an early diastolic dip followed by a diastolic plateau The level of the diastolic plateau is at a pressure roughly equal to the mean atrial pressure and peripheral venous pressure and usually at a pressure in excess of one third of the ventricular systolic pressure (168) The diastolic plateau of the right ventricular pressure curve corresponds except perhaps for some

lag in its onset with the diastolic plateau of ventricular border movement The descending limb of the early diastolic dip corresponds to the rapid filling phase of the curve of border movement. The right atrial pressure curve usually has an M shape in each cardiac cycle This is probably less specific than the ventricular pressure curve According to Hansen (67) this pattern of the right ventricular pressure curve does not occur in pericardial effusion however it does occur in fibrous myocarditis primary amyloidosis constrictive endocarditis and other states in which the pressure–volume characteristics of the ventricular wall are altered by intramural or endocardial scar in a manner comparable or identical to the change produced by pericardial scar The mechanism of the right ventricular pressure curve is not entirely clear Isaacs (81) found the same pressure pattern by recording pressure through a needle from the interior of a tennis ball which is indented and then released

The studies of Isaacs and co workers (79) support the concept, developed in recent years largely on clinical grounds that the important factor in the disturbed physiology of constrictive pericarditis is not the constriction of great veins and atria but the constriction of the ventricles Isaacs by an ingenious method for producing localized constriction in dogs found that *(1)* constriction of the left ventricle alone led predominantly to signs and symptoms of pulmonary congestion *(2)* constriction of the right ventricle produced ascites hepatomegaly and systemic venous hypertension *(3)* total constriction produced combined abnormalities *(4)* constriction of the right atrium alone had no effect *(5)* decortication of the right atrium only in dogs with total constriction had no beneficial effect. The volume–pressure curves in the ventricles of these hearts displayed graphically the impediment to diastolic ventricular filling the principal physiologic defect in most of these cases The defect in cardiac tamponade is a similar one (80)

Pulmonary capillary pressure has been elevated in most cases of constrictive pericarditis in which it has been measured Furthermore pulmonary capillary pressure pulmonary arterial diastolic pressure right ventricular end diastolic pressure and mean right atrial pressure tend to approach an identical figure

Wenckebach s theory for pulsus paradoxus (that traction on the heart and great vessels by adhesions between them and the thoracic cage interferes with emptying) has been discarded Three principal physio-

logic theories for pulsus paradoxus in pericardial tamponade have been proposed

(1) Katz and Gauchat (84) suggested that whereas normally all intrathoracic structures are subjected to the negative pressure of inspiration in pericardial tamponade this negativity affects the extra pericardial veins much more than the intrapericardial structures This discrepancy in the effects of inspiration might decrease or obliterate the pressure differential between extrapericardial veins and heart chambers which is responsible for cardiac filling Presumably this effect would be operative on both the left and the right side of the heart

2 Hitzig (73) suggested that pulsus paradoxus might be the result of an increased blood capacity of the pulmonary vasculature particularly pulmonary veins, during inspiration He quoted Starling as estimating that the pulmonary vascular bed can hold one eighteenth of the blood volume during expiration and one twelfth during inspiration Normally this slack" is almost completely taken up by the increase in the stroke output of the right ventricle accompanying the increased venous return of inspiration In cardiac tamponade on the other hand, the right ventricle is apt to be functioning close to peak output already and cannot increase its output further in response to increased venous return

3 Dornhorst Howard and Leathart (44) suggested that inspiration might so increase the filling of the right atrium and ventricle that appreciably less room would be left in the pericardial box for filling of the left ventricle

There may be a modicum of truth in each of these theories Each factor suggested may to some extent play a role in a given case but there are loopholes in all three theories The inspiratory filling of the neck veins observed in cardiac tamponade would appear to indicate an increase in filling pressure of the heart rather than the decrease which is essential to the theory of Katz and Gauchat at least as it applies to the right side of the heart If the output of the left ventricle suffers because of a robbing Peter to pay Paul" mechanism as suggested by Dornhorst and co workers why does the arterial pressure fail to fall in the patient with pulsus paradoxus due to cardiac tamponade when pressure is applied to the liver a maneuver which should *increase filling* of the right ventricle just as does inspiration? Opinion about the blood holding capacity of the lesser circulation during inspiration (159) is not unanimous

Attempts to relate respiratory variations of blood pressure to mere change of the intrathoracic pressure base line—the ventricle is casting its load from a lower pressure level during inspiration—probably can not explain the pulsus paradoxus of cardiac tamponade since the cyclic variations in intrathoracic pressure are only of the order of a few millimeters of mercury However the pulsus paradoxus which occurs with airway obstruction and with reduced expansibility or compliance of the lung can be explained on this basis

In our opinion the mechanism of pulsus paradoxus must still be considered an enigma It is intimately concerned with the physiology of the pulmonary circulation about which much remains to be learned Actually the phenomenon is of much greater physiologic interest than clinical import

CLINICAL OBSERVATIONS —There seems general agreement that Broadbent s sign is not a sound basis for diagnosis of pericardial disease Sir William Broadbent (18) does not appear to have placed as much weight on the finding of posterolateral retraction as did others who were responsible for popularizing it and he did describe certain other signs of constrictive pericarditis which even now are being rediscovered Among others he enumerated the following

Fixation of the apex beat, so that it does not alter its position in deep inspiration and expiration or in change of position of the body

Systolic depression of one or more intercostal spaces to the left of the sternum and adjacent costal cartilages

A diastolic shock may sometimes be felt on palpation with the flat of the hand over areas on the chest wall where systolic recession is present It is due to the elastic recoil of the chest wall at the commencement of diastole as soon as the pulling force exerted during the systole ceases

The area of cardiac dullness will be increased and will remain unchanged in inspiration and expiration

About the sign which specifically bears his name (19) he had this to say

Systolic retraction of the lower position of the posterior or lateral walls of the thorax may indicate the presence of a universally adherent pericardium Such retraction may however be seen though the pericardium is not adherent to the heart. In such cases the heart is usually greatly enlarged and hypertrophied from old valvular disease

Very useful in detecting constrictive pericarditis clinically is the phenomenon referred to as *diastolisches Spitzenstoss* by Skoda (147) in 1852, and as the "diastolic heart beat" by Wood (165) who has re

cently reawakened interest in this sign and elucidated its pathophysiologic basis In cases of constrictive pericarditis, a rather diffuse portion of the left midprecordium including at times the sternum or less frequently a localized intercostal area will often show a retraction or inward movement with systole and a sharp, rapid, outward movement in early diastole Under normal conditions the apical impulse rises with systole and falls away in early diastole the bulging being the result of the change in shape of the heart from ellipsoidal to globular particularly during the phase of isovolumetric contraction When the adventitious protodiastolic sound is also present it may be possible to establish that the sharp outward movement and the adventitious sound occur together The persistence of the diastolic shock after resection of the ribs led Brauer (17) to conclude that the sign is not dependent on external adhesions as had been suggested by Broadbent

The first description of the adventitious protodiastolic sound of constrictive pericarditis is usually credited to Potain (130) Although it has some auscultatory similarities to a protodiastolic gallop it should not be called a gallop because of the grave prognostic and definite diagnostic connotations of the latter term Furthermore *this sound in* constrictive pericarditis occurs earlier than a true gallop (see Plate 4) In some areas and occasionally over the entire precordium the protodiastolic sound may be greater than the valve sounds and may be confused for one of them

It should be emphasized that the protodiastolic sound while more common in constrictive pericarditis being present in at least half of the total number of cases also occurs in 20 per cent or more of cases of pericarditis with effusion but without myocardial disease (74) Atrial or presystolic gallops may also be present in pericardial effusion and at times a quadruple rhythm is encountered due to the coincidence of the two types of gallop The misinterpretation of these gallops as murmurs has several times in our experience been the source of confusion in chronic pericardial effusion

Less specific auscultatory signs in constrictive pericarditis are an *accentuated second pulmonic sound related to the pulmonary* diastolic hypertension and crunchy systolic sounds in cases of extensive pericardial calcification (55) (see Plate 4 *A*)

We are indebted to Dr Eugene Blank who while a fourth year medical student called to our attention the not infrequent occurrence of "gallops in a relatively large series of patients with acute tuberculous pericarditis seen at this hospital

Characteristically ascites is an early and conspicuous feature of constrictive pericarditis The probable reason is that the persistent nature of the venous pressure elevation which is the rule in constrictive pericarditis but unlikely in other varieties of heart failure determines deposition of retained edema fluid in the abdominal cavity as ascites The impediment to lymphatic drainage into the great veins and an increase in the production of liver lymph may be important factors in ascites formation in constrictive pericarditis (78 161) The ascitic fluid might be expected to have an unusually high protein content this might explain likelihood for fibrin deposition and the development of a "sugar coated" liver Review of available data on the protein content of the ascitic fluid in constrictive pericarditis yielded equivocal results The protein content in any one individual varied highly being related perhaps to rate of accumulation and the level of serum proteins No definite difference from the protein content of other ascitic fluids such as that of Laennec s cirrhosis could be demonstrated

On roentgenograms the heart contour is usually abnormal The superior vena cava is dilated by the prolonged and persistent elevation of venous pressure (Plate 5 *B*) Calcification occurs in about half the cases It is usually best demonstrated on lateral views of the chest and is most striking in two sites the dependent diaphragmatic portion of the pericardium and the atrioventricular grooves The heart contrary to the usual impression is often at least moderately enlarged (33 108 127) the enlargement may be due to atrial dilatation (the atria often are not proportionally involved in the constrictive process) to the thickness of the pericardial scar itself and finally to increased ventricular residual volume The last results from the frequent impediment to systolic ejection of the ventricle along with the impediment to diastolic filling The heart appears to become fixed in a partially dilated position, being able neither to contract fully nor to relax completely from that position

In many cases the etiology of constrictive pericarditis remains an enigma Tuberculosis is certainly the most frequent cause and evolution of the disease is often occult until manifestations of constriction develop (Plate 5) Hemopericardium from nonpenetrating blunt trauma to the chest occasionally without recognition at the time of the accident that injury to the heart has occurred may be followed by constrictive pericarditis (106 49) just as hemothorax may be followed by constrictive pleuritis (88) Rheumatic fever and lupus

cently reawakened interest in this sign and elucidated its pathophysiologic basis In cases of constrictive pericarditis, a rather diffuse portion of the left midprecordium including at times the sternum or less frequently, a localized intercostal area will often show a retraction or inward movement with systole and a sharp rapid outward movement in early diastole Under normal conditions the apical impulse rises with systole and falls away in early diastole the bulging being the result of the change in shape of the heart from ellipsoidal to globular particularly during the phase of isovolumetric contraction When the adventitious protodiastolic sound is also present, it may be possible to establish that the sharp outward movement and the adventitious sound occur together The persistence of the diastolic shock after resection of the ribs led Brauer (17) to conclude that the sign is not dependent on external adhesions as had been suggested by Broadbent

The first description of the adventitious protodiastolic sound of constrictive pericarditis is usually credited to Potain (130) Although it has some auscultatory similarities to a protodiastolic gallop it should not be called a gallop because of the grave prognostic and definite diagnostic connotations of the latter term Furthermore this sound in constrictive pericarditis occurs earlier than a true gallop (see Plate 4) In some areas and occasionally over the entire precordium the protodiastolic sound may be greater than the valve sounds and may be confused for one of them

It should be emphasized that the protodiastolic sound while more common in constrictive pericarditis being present in at least half of the total number of cases also occurs in 20 per cent or more of cases of pericarditis with effusion but without myocardial disease (74) Atrial or presystolic gallops may also be present in pericardial effusion, and at times a quadruple rhythm is encountered due to the coincidence of the two types of gallop The misinterpretation of these gallops as murmurs has several times in our experience been the source of confusion in chronic pericardial effusion

Less specific auscultatory signs in constrictive pericarditis are an accentuated second pulmonic sound *related to the pulmonary diastolic* hypertension and crunchy systolic sounds in cases of extensive pericardial calcification (55) (see Plate 4 A)

We are indebted to Dr Eugene Blank who while a fourth year medical student called to our attention the not infrequent occurrence of "gallops in a relatively large series of patients with acute tuberculous pericarditis seen at this hospital

due to coronary arteriosclerosis (25 67 108) Burwell recommends an exploratory thoracotomy if the differential diagnosis cannot be made by other means

McKusick and Cochran (107) described an instance of "constrictive endocarditis" which clinically closely simulated constrictive pericarditis Loeffler (95) in calling attention to this condition named it "fibroplastic parietal endocarditis" Recently Dr Gilbert Blount and Dr Glenn Clark (35) have called another case to our attention and have furthermore provided the evidence of physiologic similarity to constrictive pericarditis In the early stages of this disease the patient may show a blood eosinophilia

Many patients with constrictive pericarditis have some degree of constrictive pleuritis with diminished thoracic expansion and a reduced vital capacity Overholt *et al* (126) described a patient in whom the combination was quite clearly due to trauma and in whom combined cardiac and pulmonary decortication was performed In a case reported by Burwell and Ayer (23) the patient had constrictive pericarditis and constrictive pleuritis apparently on the basis of tuberculosis In a recent case in which this combination of visceral constriction was probably the result of a pyogenic infection in childhood combined decortication of the heart and left lung was performed by Dr J N P Johns with satisfactory clinical results

Administration of quinidine or other antidysrhythmia agent before pericardectomy seems unnecessary Periodic rests and irrigation of the heart with saline solution has sufficed when it became irregular during decortication The experience with mitral valvulotomy (43) where there has been no real evidence that digitalization increases cardiac irritability might lead to the conclusion that there is no increased risk involved in digitalizing these patients before operation On the other hand there is adequate reason to believe that digitalization in the postoperative period is beneficial We routinely administer digitalis when the patient leaves the operating room and maintain digitalization for about 2 months thereafter In cases of constrictive pericarditis the heart has in effect been in a plaster cast The myocardium like skeletal muscle in a comparable situation, undergoes disuse atrophy This atrophy is demonstrable by actual measurements of cardiac fibers (134) Digitalis helps the heart resume its normal work load Disuse atrophy accounts in part for ventricular ballooning, which occurs when the pericardial scar is released and which may take on the

erythematosus have never been conclusively identified as the cause of true concretio cordis The case reported as rheumatic in origin by McMurray and collaborators (111) was that of a patient who quite clearly had Addison's disease probably on a tuberculous basis had rheumatoid arthritis not rheumatic fever and had no unmistakable stigma of rheumatic fever such as mitral stenosis Purulent pericarditis can be followed by pericardial constriction (24) Tularemia has apparently been an occasional cause of constrictive pericarditis (83 113) Cancer en cuirasse has likewise produced this clinical and physiologic picture In 1 case, the pericardial metastasis which produced the inflow stasis was the only one from a primary breast carcinoma removed 14 years earlier (148) In the absence of even a quasi specific test for acute nonspecific pericarditis it is impossible to be certain that the case is not one of mild tuberculous pericarditis With this reservation in mind it may be stated that clinically typical cases of benign pericarditis have subsequently developed into constrictive pericarditis (25) We have observed at least one such patient both during the acute pericarditis and during his operation for constrictive pericarditis 18 months later

Mediastinal tumor is occasionally considered in the differential diagnosis of chronic constrictive pericarditis Since the inferior vena cava is not practically speaking a mediastinal structure mediastinal tumors cannot produce obstruction of both venae cavae (77) Tumors in this region can simulate constrictive pericarditis by invading the right atrium and acting as a ball-valve obstruction at that site (Plate 6) or by invading the pericardium and either inciting pericardial effusion or encasing the heart in neoplastic tissue Bronchogenic carcinoma and malignant thymoma are particularly prone to these two patterns of behaviour Mitchell and Grindle (117) have described an unusual case in which both venae cavae were thrombosed secondarily it seemed to caseous tuberculosis

Myocardial disease may be difficult to differentiate from constrictive pericarditis because of imperfect response to digitalis reduced pulse pressure "characteristic right ventricular pressure curve reduced venticular border movement pulsus paradoxus and protodiastolic gallop in both conditions (25) Primary systemic amyloidosis is a classic albeit rare example of myocardial disease which may simulate constrictive pericarditis (39 54) The same right ventricular pressure pattern (early diastolic dip and diastolic plateau) has been seen in primary amyloidosis (72) as well as in cases of fibrous myocarditis

in some cases (106 165) A possible cause for this phenomenon is relative mitral stenosis resulting from ventricular dilatation on the one hand and fibrous involvement of the atrioventricular groove on the other

The course of constrictive pericarditis without the benefit of pericardectomy is well illustrated by Roesler s (135) account of the case of Niels Finsen Danish physician who was awarded the Nobel Prize in Medicine in 1904 for the introduction of ultraviolet light as a therapeutic measure Symptoms and signs appeared when Finsen was 23 years old he died at the age of 44 His first symptoms were referable to the abdomen at which time hepatomegaly was discovered Hydatid disease was considered as he had been reared in Iceland, but the correct diagnosis was made Extensive calcification was demonstrated after Rontgen s invention in 1896 From the standpoint of physical signs it is of interest that a systolic retraction in the apical area was noted and what was interpreted as a reduplication of the second sound heard over the entire precordium creating a gallop rhythm Auricular fibrillation developed at the age of 33 Finsen made careful, pioneer observations on the relation of salt and water to his accumulation of ascitic fluid which required numerous paracenteses He was aware of the role of sodium chloride in this connection and established the abnormally low concentration of chloride in his own urine He tested the diuretic action of ammonium chloride which, according to Murchison (119) had been introduced in 1869 by Dr Wm Stewart Finsen died in 1904, a few months after receiving the Nobel award Autopsy confirmed the clinical diagnosis

Chronic mediastinopericarditis is a diagnosis formerly very popular but now scarcely ever mentioned Wood *et al* (165) outlined the following criteria for this diagnosis but stated that they had never seen such a case *(1)* The ventricles are not constricted *(2)* the pericardial scar fastens the heart to the ribs thereby increasing its work load *(3)* the combination of this load and that of some other variety of heart disease causes congestive heart failure *(4)* the heart failure is unequivocally ameliorated by the Brauer operation

Metabolic Pericarditis

The mechanism of uremic pericarditis remains unknown During severe diabetic acidosis or Addisonian crisis a pericarditis may develop which does not appear to be related to azotemia or infection

proportions of acute cardiac dilatation with cardiac standstill or ventricular rupture (108) Disuse atrophy is probably often responsible for the failure of the venous hypertension and its effects to disappear immediately as might be expected if decortication were merely a matter of removing a mechanical impediment to the circulation (69) It may explain why the heart often remains enlarged for weeks or months after pericardectomy Cardiac dilatation is probably damaging to the myocardium and judging from experiments in which the hearts of animals are placed under acute strain may result in microscopic fragmentation of the myocardial syncytium and in the development of interstitial fibrosis Digitalis restricted activity and moderately rigid salt restriction are indicated during the period of convalescence from pericardectomy

Early in the course of constrictive pericarditis the venous hypertension may not be completely fixed Venous pressure may fall to high normal values with rest and diuretic measures but usually rises abnormally with exercise Recently an 18 year old patient without previous history suggesting acute pericarditis had hepatomegaly pronounced hypoalbuminemia but no definite ascites His venous pressure fell to normal with rest and diuretics subsequently as the disease progressed venous hypertension became fixed Pericardectomy was performed and was successful

In general *hypoalbuminemia does not occur in* patients over 20 years of age When it is present in the younger patients protein concentrations promptly return to normal following pericardectomy (108)

After cardiac decortication for constrictive pericarditis the adventitious protodiastolic sound may disappear but in its place a true protodiastolic gallop slightly later in timing may appear This is particularly likely to occur during the period of postoperative ventricular dilatation We have now observed 2 cases with mid diastolic rumbles in the mitral area 18 months and 8 years respectively after operation In neither patient was the rumble noted in the first few postoperative months Neither patient had any pericardial calcification and both were operated on in their teens In both, the evidence for a tuberculous etiology is convincing The spectral phonocardiogram of one has been presented elsewhere (109) Both patients are functionally well and perform hard manual labor without particular limitation In one the heart *shows slight to moderate enlargement* in the other the heart is small Others too have observed this phenomenon on rare occasions (118 82a) A similar murmur has been heard before operation

The following cases represent some experiences with pericarditis in severe diabetic acidosis Pericarditis due to infection or following myo cardial infarction may of course occur in diabetes

CASE 7—J J a Negro boy 18 who had had 18 admissions to this hos pital for treatment of diabetic acidosis was admitted 18 hours before death in severe acidosis Despite vigorous treatment death occurred during intra venous injection of potassium given when muscle paralysis developed Autopsy revealed mild acute interstitial pericarditis

CASE 8—C C a Negro woman 54 was admitted in diabetic coma with profound acidosis A pericardial friction rub not previously present was heard 16 hours later Rehydration and correction of the acidosis had been accomplished and the nonprotein nitrogen was normal No electrocardio graphic changes or enlargement of the cardiovascular shadow had ever been found The rub persisted for 6 days The white cell count was 39 000 per cubic millimeter and the patient had complained of a sore throat This may have been a case of "benign idiopathic pericarditis" which played a role in precipitating the acidosis

CASE 9—M B a white man 26 was admitted in diabetic acidosis About 8 hours later a pericardial friction rub was heard during systole only this persisted for almost a week The nonprotein nitrogen was normal On ad mission the icteric index was 25 the subsequent course was consistent with the diagnosis of infectious hepatitis

CASE 10—L C a Negro boy 17 was admitted in severe diabetic acidosis A loud palpable substernal crunch limited to systole was heard and persisted for 8 hours Nausea vomiting substernal burning and peri umbilical pain following the ingestion of a quart of "soda pop" had de veloped a few days before admission Mediastinal emphysema was a pos sibility in this patient

Evaluation of the pericarditis in Addison s disease and diabetes is difficult In both conditions it may represent an intercurrent infection Recently Conley (36) called to our attention 2 cases of agnogenic myeloid metaplasia in which fibrinous pericarditis occurred in one no etiologic basis was discovered at autopsy in the other the patient recovered after resorbing a sizeable pericardial effusion

PERICARDITIS SECONDARY TO OTHER CARDIOVASCULAR DISEASES ESPECIALLY POSTINFARCTIONAL (EPISTENOCARDIC) PERICARDITIS

Leaking of a dissecting aneurysm of the aorta into the pericardial sac occasionally creates a clinical picture suggesting primary pericar ditis

The pathogenesis of the chronic pericardial effusion of myxedema (85) also is not clearly understood

The following case histories illustrate the clinical features of the pericarditis which may be associated with Addison's disease Obviously when Addison's disease results from tuberculosis of the adrenals tuberculous pericarditis may also develop This etiology was excluded in the cases described below as was pyogenic pericarditis It would seem probable that this association of pericarditis and adrenocortical insufficiency is more than coincidental

CASE 3—O Q a white man 62 was found to have Addison's disease in 1932 and was treated with supplementary salt He was well until the morning of death when there was sudden onset of severe pain over the left lower precordium moving later to the epigastrium The temperature rose to 103 F and he became mildly delirious He died in his sleep in the late evening At autopsy the pericardium contained 200 cc of fluid and a fibrinous exudate covered both the parietal and the visceral pericardial surfaces The adrenal failure was due to idiopathic atrophy

CASE 4—M S a white woman 36 had Addison's disease which on autopsy (in 1932) also proved to be due to idiopathic atrophy of the adrenals She was well until the night before death when she complained of dyspnea and pain over the heart She was forced to sit up several times The following morning she remained in bed but felt well She was found dead in bed 30 minutes after being last seen Autopsy revealed fresh fibrinous pericarditis

CASE 5—C K a man 22 died in 1932 of Addison's disease due to adrenal atrophy He had voluntarily stopped taking supplementary salt his only medication 3 weeks before death A cold with coryza and sore throat followed by cough pain in the chest anorexia and extreme weakness developed 3 days before death These complaints continued with mild variations in severity during the 3 days He died in the ambulance on the way to the hospital Autopsy revealed a serofibrinous pericarditis

CASE 6—A S a white man 41 had Addison's disease which on autopsy examination proved to be the result of adrenal tuberculosis In the previous 8 months he had had DCA pellets implanted on 2 occasions On Aug 2 1942 he awoke with a sore throat and fever and chills vomiting and pain over the heart developed His temperature remained elevated for several days (103 6 F) then fell to near normal On the thirteenth day in the hospital it again rose pulsus paradoxus developed and he complained again of precordial pain Death occurred on the fourteenth day Autopsy revealed extensive sterile pericarditis with a large effusion The exudate was profuse and thick consisting of fibrin and inflammatory cells In some places polymorphonuclear leukocytes were numerous No bacteria could be stained and no hilar lymph nodes appeared to be feeding the pericardium with tuberculous material

aspiration in all cases of hemopericardium following stab wounds (15 51 130) while others (99) believe that in all cases exploration and the indicated corrective surgery should be performed resorting to aspiration as an immediate lifesaving procedure By following the first view thoracotomies can be avoided in many instances On the other hand if thoracotomy is performed secondary hemorrhages from laceration of the heart can be avoided and leaks in the great vessels identified and repaired Selection of cases for thoracotomy as opposed to aspiration treatment is not easy but a dogmatic approach would seem a poor one The decision should be based on the findings in each individual case

We have encountered transient pericardial friction rubs following roentgen therapy to the thymus in myasthenia gravis and to the mediastinum for lymphoma Massive chronic pericardial effusions have been reported following such treatment for carcinoma of the breast (16) and for thyrotoxicosis (138)

A number of deaths from cardiac tamponade have followed sternal marrow puncture (143) In most of the cases death has occurred within less than 30 minutes of the time the procedure was performed The presence of a hemorrhagic diathesis obviously increases the risk of this complication In one patient pericardial fluid was aspirated at the time of sternal puncture Pericardial friction rubs and systolic crunches of mediastinal emphysema are not uncommon after sternal puncture If the sound occurs only during systole it is probably an indication of mediastinal emphysema rather than of pericarditis however this is not a certain distinction

PERICARDIAL CYSTS AND DIVERTICULA

The great increase in mass x ray surveys on the one hand and the advances in thoracic surgery on the other have broadened the experience with these interesting anomalies (21 50 93 94 121) Pericardial cysts appear to be of the same general nature as pleural and probably mesenteric cysts All may be termed celomic cysts It may be difficult to differentiate a pericardial from a pleural cyst, although the latter are much less common only some five having been reported in the literature (40)

The characteristic location for pericardial cysts is at the angles or points of junction of the parietal and visceral pericardium the commonest site being the cardiophrenic angle (Plate 7) However we have

We have recently observed a 30 year old patient with Marfans syndrome who five years before death had his first dissection of the aorta with leakage into the pericardium A friction rub persisted for about two weeks Treatment for presumed tuberculous pericarditis was given Subsequently inequality of the blood pressure in the arms and a basilar diastolic murmur developed Two years before death there occurred a second episode of chest pain accompanied by evanescent friction rub Autopsy revealed an old dissection of the ascending aorta and histologic changes in the media typical of Mar fans syndrome Although survival for several years after dissection is not uncommon, survival after rupture into the pericardium must be exceedingly rare The simulation of primary pericarditis is of much interest

*Pericardial friction rubs occur frequently with bacterial endo*carditis and with coronary embolism either infected or bland Most important, from the standpoint of incidence is the pericarditis associated with myocardial infarction The character of the pain and the electrocardiographic changes which may be useful in distinguishing primary pericarditis from postinfarctional pericarditis have already been discussed

Intrapericardial bleeding is a risk of anticoagulant therapy for myo cardial infarction (59 139) and for other types of pericarditis mis diagnosed *as myocardial infarction (90 103 106 129)* Izzo *et al* (82) suggest that watch be kept for the following signs during treat ment of cases of myocardial infarction with anticoagulants *(1)* pro longed and persistent or recurrent friction rub *(2)* recurrent chest pain without renewed electrocardiographic evidence of myocardial injury *(3)* circulatory collapse with drop in blood pressure *sudden* hepatomegaly venous engorgement *(4)* sudden unexplained anemia and *(5)* clinical or x ray evidence of enlargement of the cardiovascular silhouette

Pericarditis Due to Physical Agents

Hemopericardium is a well recognized complication of blunt non penetrating trauma to the chest, such as that inflicted by the steering wheel in an automobile accident Not infrequently the trauma is for gotten or considered inconsequential (89 106) and a diagnosis of myocardial infarction is made Stab and gunshot wounds may be com plicated by hemopericardium Some favor treatment by repeated

aspiration in all cases of hemopericardium following stab wounds (15 51 130) while others (99) believe that in all cases exploration and the indicated corrective surgery should be performed resorting to aspiration as an immediate lifesaving procedure By following the first view thoracotomies can be avoided in many instances On the other hand if thoracotomy is performed secondary hemorrhages from laceration of the heart can be avoided and leaks in the great vessels identified and repaired Selection of cases for thoracotomy as opposed to aspiration treatment is not easy but a dogmatic approach would seem a poor one The decision should be based on the findings in each individual case

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seen a case in which the cyst was apparently derived from the most superior reflections of the pericardium appearing almost at the level of origin of the innominate artery

Progressive enlargement of these cysts occurs as they fill with fluid In one case a cyst became apparent between two roentgen studies of the chest a year apart. In another instance the patient was turned down by Selective Service 10 years before thoracotomy was performed The crystal clear fluid has been responsible for their designation as "spring water cysts" (27)

All cysts should be removed since their diagnosis is never completely certain and they may produce vague thoracic symptoms as a result of progressive enlargement The difficulties of diagnosis are illustrated by Bates and Leaver (9) who reported 5 cases of celomic cysts together with 5 examples of other intrathoracic lesions (lipoma, dermoid cyst partial eventration of the diaphragm etc) which produced a virtually identical roentgenographic picture Laminagrams will occasionally permit differentiation of a pericardial cyst from a ventricular aneurysm (Plate 7 *A)* A teardrop configuration with extension of the cyst into the interlobar fissure on the right may simulate an interlobar empyema (136) Herniation through the right foramen of Morgagni may also create confusion Brocard *et al* (20) performed pneumoperitoneum in one such case in order to exclude the possibility *of diaphragmatic hernia*

These cysts rarely calcify (157) Conceivably they might become infected and thereafter undergo calcification but when calcification is demonstrable a dermoid cyst or some other lesion should be suspected

Essentially a diverticulum of the pericardium is probably the same as pericardial cyst representing incomplete cyst formation (14 66) Mazer (101) described a true diverticulum which even at operation was thought to be a cyst until it was found that its contents could be expressed Cushing (41) reported such a defect which presented as an asymptomatic mass in the right cariophrenic angle on routine roentgenography A bulge of the anterior chest wall developed 5 years later in the area overlying the position of the mass revealed by x ray aspiration disclosed tuberculous material and injection of air showed free communication with the pericardial sac Calcification had developed in the diverticulum It seems likely that this was a case of pericardial *diverticulum with superimposed tuberculous pericarditis*

Hernia of the pericardium is a closely related disorder Gromet and

Steinberg (62) described a bizarre roentgenographic picture in which a very conspicuous but relatively localized outpouching occurred at the upper left extremity of the pericardial reflection when the patient had one of his recurrent pericardial effusions

LESS COMMON DISORDERS OF THE PERICARDIUM

INVOLVEMENT IN "ALLERGIC GRANULOMATOSIS"—Involvement of the pericardium in serum sickness and in other anaphylactoid states is well known A condition akin to these disorders and to periarteritis nodosa is one which has been called allergic granulomatosis (34) The victim of this disorder usually has asthma as a conspicuous feature at some stage Blood eosinophilia is likely to be impressive Pulmonary infiltrations or pseudotumors are common The morbid anatomy is characterized by granulomatous masses containing many eosinophils The following case illustrates this type of pericardial involvement

CASE 11—A W a white woman 38 had had severe bronchial asthma for about 5 years before her death in status asthmaticus and had had evanescent skin eruptions several times during this period No signs of pericardial involvement had been elicited during life Autopsy revealed a peculiar pericarditis with eosinophils plasma cells and multinuclear giant cells dominating the cellular infiltrate Granulomatous foci were present in the myocardium of the left ventricle and there was eosinophilic hyperplasia of the bone marrow

INVOLVEMENT IN RHEUMATOID ARTHRITIS—Clinically pericarditis is an uncommon manifestation of rheumatoid arthritis but pathologically pericardial involvement occurred in 20 of 47 cases that came to autopsy (8) Only in 1 of these cases could a definite diagnosis of rheumatic heart disease be made In 2 cases the pericardium showed nodules indistinguishable from subcutaneous nodules of rheumatoid arthritis Nodules of the pericardium may be demonstrable on chest roentgenograms (110)

CHOLESTEROL PERICARDITIS—About 8 cases of so called cholesterol pericarditis of the primary type have been reported (1 2 42 71 112 114 151 160) and a ninth case has been studied by Genecin (57) It is a variety of chronic pericardial effusion in which the fluid has the appearance of dilute gold paint The sheen is due to the presence of myriads of cholesterol crystals There is usually no accompanying elevation of the serum cholesterol concentration Furthermore some of the cases have shown no increase of cholesterol concentration in

the pericardial fluid in these cases it would seem that a change in the physicochemical state resulting from the absence of suspending lipoproteins favored the crystallization of the cholesterol

It has been suggested that disrupted erythrocytes might be the source of the cholesterol which once crystallized out, is probably removed very slowly from the pericardial sac as demonstrated by the experiments of Drinker and Field (45) in rabbits and of Stewart and associates (154) in man This might in itself cause an irritative effusion long after the primary cause is no longer operating

In the case reported by Ada and co workers (1) the pericardium removed at thoracotomy showed an inflammatory process with occasional foreign body giant cells Although Yu *et al* (169) did not state that in their case the fluid ever had the typical character of cholesterol pericarditis biopsy of the pericardium revealed deposits of cholesterol crystals together with foreign body giant cells

Hypothyroidism as a cause is probably rare (75) In Genecins case (57), a familial factor is suggested by the fact that an asymptomatic pericardial effusion was discovered incidentally in a brother Both patients were about 20 years old It seems possible that any pericarditis which is accompanied by a hemorrhagic effusion (traumatic tuberculous idiopathic postinfarctional) may be followed by cholesterol pericarditis The characteristic gold paint appearance of the fluid usually disappears after a few pericardiocenteses and repeated pericardiocenteses seems to help in clearing the effusion

The pathogenesis is probably similar to that of cholesterohydrothorax of which tuberculosis is thought the more frequent cause (153) Chylopericardium which may occasionally result from traumatic (3 167) and other types of thoracic duct obstruction is a different entity

PERICARDIAL EFFUSION IN CONGESTIVE HEART FAILURE —A larger pericardial effusion may occur in congestive heart failure than is often realized This may contribute significantly to the enlargement of the cardiovascular silhouette In a case of right atrial myxoma seen at this hospital in 1952 (6) operation for suspected constrictive pericarditis had been performed in 1946 at that time the pericardial sac contained 300 to 400 cc of fluid without any evidence of inflammation

CHRONIC IDIOPATHIC PERICARDIAL EFFUSION —It is appropriate to conclude this survey with a discussion of a group of cases which although fortunately not common present most difficult diagnostic and therapeutic problems In these cases massive pericardial effusion may recur

over a period of several years The patient may be relatively asymptomatic or may suffer from repeated bouts of cardiac tamponade

Tuberculosis trauma systemic lupus erythematosus chylopericardium and myxedema are some of the conditions which must be considered in these cases Myxedema can as a rule be excluded easily by modern methods for evaluating thyroid function Trauma with chronic irritation of the pericardium and perpetuation of the effusion by breakdown products of blood appears to have been the basis for a pericardial effusion of several years standing in 1 case (7) Chylopericardium is usually distinguished by the character of the fluid and the associated chylothorax but a mistaken diagnosis of tuberculous or other type of pericarditis has been made (63) The appearance in the pericardial sac of lipophilic dyes such as Sudan III, administered by mouth may help to establish the diagnosis of chylopericardium Tuberculosis and systemic lupus are each probably responsible for occasional cases of chronic pericardial effusion which resist definitive etiologic diagnosis Cholesterol pericarditis is of course also in this category

After all diagnostic possibilities have been exhausted occasional cases are left in which no cause is ever identified even by autopsy In some cases pericardectomy has been resorted to as a means of preventing recurrent and life endangering tamponade (46 110 169)

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The Nephrotic Syndrome

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MANY PATIENTS complaining mainly of oedema are found to be passing appreciable amounts of protein in the urine This association has long been recognized as simple boiling of the urine followed by the addition of weak acid will demonstrate the presence of protein and even roughly grade the concentration present In some of these patients further abnormalities cannot readily be detected by physical examination or by urine testing in others such conditions as congestive cardiac failure chronic infections or some degree of haematuria—to mention only a few commonly associated disturbances—are found This has led to the acceptance of the term "nephrotic syndrome" to cover a disease state the primary cause of which differs from case to case but in which a fairly constant relationship is found between *(1)* the urine and plasma changes and *(2)* the plasma changes and the oedema This implies that the symptomatic management of these patients as a group can be validly discussed although it should not be forgotten that complete diagnosis prognosis and radical treatment are not within reach until the exact cause of the syndrome has been established in each case

The essential features of the nephrotic syndrome are oedema pronounced proteinuria, and hypoalbuminaemia In patients with certain forms of renal disease with which the syndrome may be associated there may be hypertension excessive numbers of red blood corpuscles

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deficiency occurs only in the most severe stages whereas anaemia and diminished working ability may persist even after oedema has been eliminated

PAPER ELECTROPHORESIS FOR STUDY OF URINARY AND SERUM PROTEINS

Before discussing the biochemical changes in the plasma and urine in the nephrotic syndrome it is worth stressing the importance of technical innovations in advancing knowledge of this group of diseases Berglund Scriver and Medes (4) give a good historical background for the methods used in studying proteinuria and, later the plasma changes accompanying renal disease In 1935 serum could only be separated conveniently into two entities "albumin" and "globulin," by salting-out procedures Soon afterward some electrophoretic analyses of sera and urines from nephrotic patients were reported (42, 44) these clearly marked a major step forward But only during the last 3 to 4 years have repeated electrophoretic determinations become generally available as simplified techniques on filter paper strips were developed These are all derived from the work reported in 1950 by von Turba and Enenkel (74) Many minor improvements have been made recently and described in reports from various centres The advantages of paper electrophoresis and the details of the quantitative technic used in our Department have been described by Hardwicke (28) Not only are very small samples sufficient but the results in nephrotic serum especially are in some respect more accurate than those obtainable by the classical methods of separation using expensive and cumbersome apparatus The values obtained by paper electrophoresis and by the classical Tiselius method differ somewhat in detail on the paper protein is estimated from its dye binding properties while in the classical U tube method both lipid and protein contribute —a distinction which becomes specially significant with the exaggerated lipid content of some globulin fractions in nephrotic serum It is also important to realize that the albumin values reported from electrophoretic determinations are lower than the older salting-out albumin figures which include appreciable amounts of electrophoretic globulin (Minor differences may also be reported from different laboratories using paper electrophoresis unless agreement is obtained about corrections to be applied for loss of albumin by "tailing" on the paper)

in the urine electrolyte disorders and even persistent retention of nonprotein nitrogen Or the *syndrome may be found in association* with circulatory disorders (e g constrictive pericarditis renal vein thrombosis) as a complication of diabetes or of infections such as chronic tuberculosis or syphilis or following certain forms of intoxication In the future perhaps all examples of the nephrotic syndrome may be assignable to groups such as these but at present many must be given the label "nephrotic syndrome" without qualification This last group of patients is specially worthy of study to try to discover the underlying cause of the syndrome It is also important that in this group of nephrotic patients there are fewest complications to distract attention from the essential features of the syndrome

CLINICAL FEATURES

Patients of *all ages and both sexes may be affected* Oedema is the presenting sign in severe cases ascites and pleural effusions are present, and may produce some dyspnoea Massive oedema may even *spread up to the level of the throat* and *threaten suffocation* especially if the patient sleeps in a flat position Oedema of the periorbital tissues does occur and often follows a period of weeping or recumbency These patients commonly also complain of malaise and incapacity for normal work or exertion Recurrent headaches may be noted in the absence of hypertension Some loss of appetite is common, and periodic vomiting especially in the mornings may occur Fever is absent but some elevation of the pulse rate is found from time to time The patients are usually pale and anaemia is often present the pallor may exceed that seen in patients with the same haemoglobin level from simple anaemia The nutritional status is not readily appraised as oedema obscures weight changes Subcutaneous fat is not usually reduced but loss of muscle substance may often be detectable A few patients show poor growth of hair and nails the hair losing its natural texture *and a ridge sometimes* being apparent in the nails as they grow during convalescence Signs of vitamin deficiency are absent Overt endocrine disturbances are not usual amenorrhea may occur in severely *affected women but normal menstrual periods* and normal development at puberty are more usual These clinical features are listed and an attempt will be made to correlate them with the underlying features of the syndrome *now to be discussed Judging by the* sequence of events during recovery from the syndrome frank nutritional

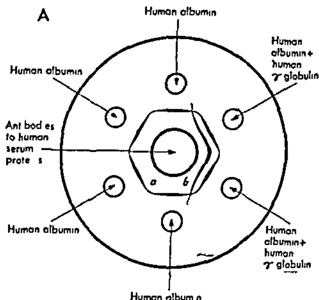
By electrophoresis one can readily distinguish five fractions in nephrotic serum albumin α_1, α β, and γ globulins. These are the same fractions and have essentially the same mobilities as the five fractions which can be detected in normal serum (though some tendency for α and β globulin bands to coalesce may be seen and occasionally a fast moving "pre albumin fraction is apparent) But in nephrotic patients the concentrations of each fraction are characteristically altered The fraction most altered quantitatively is the serum albumin which is always markedly reduced in concentration some times to 0.5 Gm per 100 ml instead of the normal concentration of about 4 Gm per 100 ml Since even in such severely affected patients the total plasma protein is seldom much below 4 to 5 Gm per 100 ml the electrophoretic albumin-globulin ratio in confirmation of earlier work, is always greatly reduced

SOURCE OF URINARY PROTEIN

Electrophoresis of urinary protein discloses the same five fractions with the same mobilities as of the protein found in the serum though again in greatly different proportions One fraction the α globulin is only detectable in the urine of some patients by loading the paper rather heavily with protein This apparent identity in the nature of electrophoretic components in normal serum nephrotic serum and nephrotic urine strongly supports the correctness of the now classical theory that urinary protein is derived from abnormal losses of qualitatively normal serum proteins by a malfunctioning kidney, This view is reinforced by other evidence By feeding glycine containing the heavy isotope N^{15} Spector (68) was able to label quantitatively the serum proteins of 3 nephrotic patients for periods of several days Albumin recovered from numerous consecutive urine samples when compared with corresponding specimens of serum albumin showed a closely similar rise and fall in isotope content This resemblance was striking in that the isotope content of other serum proteins—the serum globulins—was in each case widely different from that of the corresponding albumin

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different antigens cross over without joining as at *b* *B* serological identity of albumins from urines and sera note junctions between all precipitin bands illustrating serological identity of antigen (Results obtained by Dr P G H Gell (21))



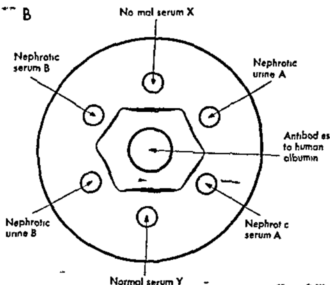


FIG 1 —Precipitin reactions in agar plates demonstrating serological identity of urinary albumin with albumin from normal and nephrotic serum Circles represent cavities cut out of agar in Petri dish to contain antigen and antibody solutions *A* demonstration of principle precipitin reaction bands between anti gens and mixed antiserum Bands due to same antigen join as at *a* those due to

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SOURCE OF URINARY PROTEIN

Electrophoresis of urinary protein discloses the same five fractions with the same mobilities as of the protein found in the serum though again in greatly different proportions One fraction the α_2 globulin is only detectable in the urine of some patients by loading the paper rather heavily with protein This apparent identity in the nature of electrophoretic components in normal serum nephrotic serum and nephrotic urine strongly supports the correctness of the now classical theory that urinary protein is derived from abnormal losses of qualitatively normal serum proteins by a malfunctioning kidney This view is reinforced by other evidence By feeding glycine containing the heavy isotope N^{15} Spector (68) was able to label quantitatively the serum proteins of 3 nephrotic patients for periods of several days Albumin recovered from numerous consecutive urine samples when compared with corresponding specimens of serum albumin showed a closely similar rise and fall in isotope content This resemblance was striking in that the isotope content of other serum proteins—the serum globulins—was in each case widely different from that of the corresponding albumin

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different antigens cross over without joining as at *b* *B* serological identity of albumins from urines and sera note junctions between all precipitin bands illustrating serological identity of antigen (Results obtained by Dr P G H Gell (21))

The problem can also be put before the immunologist In a test depending on the diffusion of antibodies (e g rabbit anti human serum proteins) horizontally through agar toward specimens of antigen (e g human serum), a precipitate forms at the zone of optimal proportions (21) When two antigens are serologically indistinguishable the lines which form opposite adjacent specimens (e g of normal serum) join in an angle and no crossover occurs (Fig 1 A) An experiment in which normal sera, nephrotic sera, and nephrotic urines from 2 different patients were set up so as to be adjacent and opposite to a rabbit anti human serum albumin showed angular junctions in every case (Fig 1 B) (The details of a similar technic and of its use in combination with electrophoresis have been described by Grabar and Williams (25)) This proof of serological identity is not of course proof of absolute identity Nevertheless if differences between nephrotic and normal human serum albumin exist but fail to show on serological or electrophoretic analysis they are likely to be small (Differences reported so far from various sources (14 48) could all be attributed to contamination of albumin specimens with varying amounts of globulins) Furthermore these hypothetical differences are not the cause of the protein loss and so involve introducing an additional postulate for when normal human albumin is infused into a nephrotic patient temporarily raising the concentration of albumin in his serum a corresponding increase in urinary albumin occurs without any increase in the number of fractions detectable by electrophoretic analysis In other words normal serum albumin apparently leaks through the nephrotic kidney The quantitative relations after such infusions will be discussed in a later section since they appear to throw useful light on the nature of the functional defects in the kidney Meanwhile the relation between the spontaneous level of serum albumin concentration and urinary albumin loss will be described as constituting the first stage in assessing the impairment of the protein *retaining power of the kidney and at the same time* the body s rate of production of albumin

URINARY LOSS OF ALBUMIN AS MAIN CAUSE OF HYPOALBUMINAEMIA

Hypoalbuminaemia can theoretically arise from deficient production from excessive loss (e g in the urine) or from excessive utilization within the body This last alternative seems unlikely in the nephrotic

syndrome especially since the output of urea the normal end product of protein metabolism is lower than normal In an earlier publication (70) it was suggested that internal utilization of albumin might be proportional to the serum albumin concentration This hypothesis—as yet it is no more than that—was invoked to explain clinical facts and measurements On a steady dietary intake and at rest in bed a nephrotic patient often maintains for several consecutive weeks a steady level of serum albumin while losing a fairly constant amount of albumin (and of total protein) in the urine each day The serum albumin may for example remain at 0 8 Gm per 100 ml with a daily loss of 0 2 Gm albumin per kilogram normal body weight (here and elsewhere this term is used to connote the patient s weight before the development of his illness or after convalescence and elimination of oedema) This steady state implies a balance between production and utilization plus urinary loss In the normal person evidence from isotope studies indicates that the daily production of albumin is about 0 25 Gm per kilogram body weight (73) and is balanced by a corresponding rate of utilization Obviously if this normal rate of production continues in the nephrotic patient cited as an example utilization must be less than normal—presumably of the order of (0 25 – 0 20) = 0 05 Gm per kilogram per day i e about one fifth of the normal figure This implies that utilization is reduced in proportion to the reduction in serum albumin concentration to one fifth of the normal value of 4 Gm per 100 ml i e to 0 8 Gm per 100 ml An alternative explanation would be that utilization had remained normal while production had risen to (0 25 + 0 20) = 0 45 Gm per 100 ml i e to nearly double the normal rate

The correct choice between these alternatives should be clear from isotope studies of nephrotic patients For this purpose N^{15} seems specially suitable and the results obtained by Spector (68) are of great interest With a standard dose of N^{15} (10 mg per kilogram expected weight) to 1 normal and 3 nephrotic children rapid incorporation of the element into serum albumin was observed the peak concentration occurring some 8 hours after dosage This peak varied from a level of 0 06 units (atom per cent excess N^{15}) in the control patient with a serum albumin of 3 6 Gm per 100 ml to 0 52 units in the most severely affected nephrotic with a serum albumin of 0 3 Gm per 100 ml In other words the peak level was about inversely proportional to the serum albumin concentration Spector is cautious in drawing direct

conclusions from these findings but they seem consistent with the view that in these children who were on a good diet and in positive nitrogen balance the rate of albumin production was approximately normal and that the high peak levels of N^{15} were due to the newly formed albumin mixing with a greatly reduced "pool" of albumin After passing a peak level the degree of labeling of the serum albumin declined more rapidly in these nephrotic patients than in the normal child the decline was most rapid in the patient with the heaviest proteinuria and quantitative considerations are consistent with the idea that the urinary loss accounted for this finding

The statement that albumin production appears to be normal in some patients with the nephrotic syndrome while utilization is not increased but probably reduced implies that the main cause of the hypoalbuminaemia is the urinary loss of albumin This is not to say that all nephrotic patients taking various levels of diet and probably differing in other ways also have normal rates of albumin production The problem may be considered by charting daily loss of albumin in the urine (Gm /kg normal body weight/day) against serum albumin concentration in two ways (1) in a group of patients (70) and (2) using several determinations on individual patients in whom albuminuria is diminishing during convalescence (30) In either case though the points are scattered a definite relationship is seen, the level of serum albumin tending to be more reduced the greater the albuminuria By and large the serum albumin level seems to be determined by the failure of the protein retaining power of the kidneys But sometimes instead of increase in albuminuria being accompanied by a fall in serum albumin the reverse occurs—a slight rise in the serum level This may be seen for instance some while after a patient is transferred from a subsistence diet to an ample intake of protein (it also occurs transiently after albumin infusions as already mentioned) With such a dietary change it seems likely that the response observed is due not to any further loss of renal protein retaining power but to an increase in albumin production perhaps from a low to a normal rate If so the question arises whether even higher rates of production could occur on optimal diets which might further slightly increase the serum albumin level This question is not academic since the borderline between the continuance or disappearance of oedema may be critically dependent on slight changes in albumin level

The chart in Figure 2 is given to clarify this point of view on it the relation between urinary albumin loss and serum albumin concentra

tion can be plotted for any individual patient Boundary lines run down from left to right classifying patients in terms of their probable rates of albumin production as being of high, low or normal range (i e within 10 per cent above or below the estimated normal values) Other dotted lines charted from results (29) obtained within 48 hours of albumin infusions (during which the renal state is assumed to remain

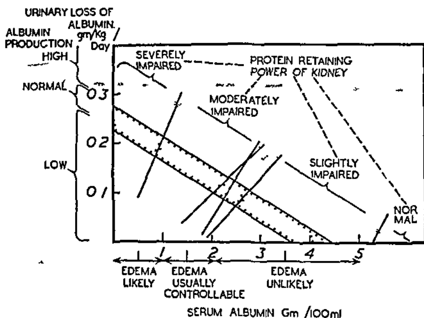


Fig 2—*Method of estimating level of albumin production (high normal or low)* and protein retaining power of the kidney (severely moderately slightly impaired or normal) from serum albumin concentration and urinary loss of albumin in patients in steady states

constant) may be used to grade patients in terms of the protein retaining power of their kidneys as being severely impaired moderately impaired slightly impaired or normal

Figure 2 is put forward for critical comment and should be regarded as liable to revision in the light of further experience In practice urinary albumin losses are estimated from the total protein content (biuret or Kjeldahl method) and electrophoretic albumin analyses on 24 hour samples If possible three separate collections are used to check not only the accuracy of the determinations but also that the

patient is in a steady state This usually limits the selection of patients to those at rest in bed The contour lines chosen for albumin production assessment are based on a normal level of serum albumin of 4 Gm per 100 ml and the figure of 0.25 Gm per kilogram per day for normal albumin production (73) Clearly this figure is likely to vary somewhat depending on whether the patient is thin or obese It also depends on the theory described above, and as yet unproved that utilization varies directly with serum albumin concentration The dotted lines for classifying the protein retaining power of the kidney show some variations not only in position but also in slope This property of the kidney depends on at least three variables the leakiness of the glomerulus the reabsorbing power of the tubules for protein and the glomerular filtration rate As these apparently vary independently from patient to patient and probably also at various stages of disease only a broad assessment of this kind of renal function can be deduced from the chart

In this discussion serum albumin levels have been related to albumin loss as being a logical procedure In fact an equally satisfactory relationship has been found between serum albumin level and daily loss of total protein in the urine (30 70) As the proportion of albumin in the urinary protein varies only between about 50 per cent and 80 per cent in all patients and within less wide limits in any individual either relationship can probably be used for the approximate kind of assessments at present available

In spite of such criticisms the chart in Figure 2 may be of clinical value particularly in assessing the prospects and results of treatment Serial estimations on a number of patients lead to the conclusion that the degree of impairment of renal protein retaining power changes only gradually at least if the change is of more than minor degree Changes from severe to moderate impairment are seen during convalescence and presumably these might be accelerated by the use of drugs like ACTH Other patients show an increased impairment during terminal illness In patients with subacute nephritis complicated by the nephrotic syndrome renal failure or fatal hypertension may supervene without any increased impairment of protein retaining power in accordance with established teaching In contrast with the slow tempo of changes in renal condition the level of albumin production as estimated from Figure 2 is prone to much greater fluctuation In a recently studied series 7 of the 14 patients could be considered to have low values of production when first seen and in 3 of these dietary

treatment was accompanied by a change to normal or high values Little experience of the effects of varying treatment as assessed in this way is yet available but it is interesting to note that high levels of protein feeding have induced high values of albumin production in some cases for long periods

URINARY LOSS OF PROTEIN OTHER THAN ALBUMIN AND RELATED SERUM CHANGES

Although albumin usually constitutes at least one half and common ly three fourths of the protein lost in nephrotic urine the remainder includes all the electrophoretically distinguishable globulin fractions By staining paper strips for lipid the urinary protein in marked con tradistinction to serum *is found to be substantially lipid free, lipo* proteins therefore are either not filtered through the glomerulus or as seems less likely, are broken down in the tubules Fibrinogen also is not usually found in the urine The concentrations of α β and γ globulins in urine though appreciable never equal those of albu min but except in severe nephrosis these globulins are also less con centrated than albumin in the serum A satisfactory way of judging the *loss of these fractions is by estimating their clearances (amount lost* per minute divided by serum concentration) and then calculating the clearance of each fraction as a percentage of the albumin clear ance This form of expression is especially suitable and is not apt to be affected by changes in the serum concentrations of the different con stituents Expressed in this way a definite order of relative transmis sion by the kidney becomes apparent (29)

$$\text{albumin} \simeq \alpha > \beta \simeq \gamma > \alpha \text{ globulin}$$

As previously pointed out (70) this order corresponds with currently accepted estimates of molecular size Some difficulties become appar ent in particular some if not all of the electrophoretic fractions con tain more than one entity The β globulin fraction for example is made up of the low molecular weight iron and copper carrying globu lins as well as a high molecular weight lipoprotein The latter appar ently escapes into the urine little or not at all while the metal carrying globulins are freely lost (12 53)

As excessive urinary loss of albumin appears to be the main cause of hypoalbuminaemia so in the case of the globulins most freely excreted (α_1 globulin γ globulin, β metal-carrying globulins) some degree of

depletion in the plasma might be anticipated This is in fact found, for these proteins are reduced in nephrotic sera Furthermore the degree of depletion of these fractions is greater in the more severely affected patients with more proteinuria and hypoalbuminaemia

The functional results of globulin depletion may eventually be shown to be clinically as important as the albumin depletion. γ Globulin depletion is presumably related to the notorious tendency of nephrotic patients to develop infections The functions of α_1 globulin(s) are poorly understood though certain protein linked hormones apparently fall into this category Protein bound iodine is reduced in nephrotic sera and excessive losses occur in the urine (60) But according to Recant and Riggs (60) the quantities lost are not sufficient to account for the low basal metabolic rate found in this syndrome and tests of thyroid function with radioactive iodine give essentially normal results Of particular interest are the reduced levels of the iron and copper carrying globulin (transferrin, caeruloplasmin) for the recurrent anaemia of the nephrotic patient presents a serious therapeutic problem Cartwright et al (12) have carried out careful studies in a group of patients with proteinuria showing that both plasma copper and plasma iron are reduced on the average to about half the normal value Low plasma copper was not found in patients with hypoalbuminaemia due to other causes Urinary loss of both metals was abnormal and could be correlated with the degree of proteinuria The iron binding capacity of the plasma was reduced even more than the iron content so that whereas only about one third of the capacity is taken up by iron in the normal subject about two thirds saturation was found in the nephrotic patient Unfortunately these workers found that the anaemia did not respond to administration of copper Further work may show that excessive urinary losses lead to deficiencies of other factors also required for erythrocyte production

INCREASED PLASMA CONSTITUENTS IN NEPHROTIC SYNDROME

In nephrotic patients in whom the serum albumin is only about 25 per cent of normal (1 Gm per 100 ml) fibrinogen and cholesterol levels are often 300 per cent of normal α globulin is on the average more than 200 per cent of normal, and total β globulin about 150 per cent of normal (29 70) In view of the known reduction in β metal carrying globulins the last figure probably represents an even greater

↓b a, β (lipomaker)

increase in the β lipoprotein level. Similar changes though less marked are seen with less severe degrees of hypoalbuminaemia, while even greater increases are usual in more severely affected patients The proteins which are increased above normal in nephrotic plasma are the larger molecules which escape less readily into the urine They contribute to the greatly raised erythrocyte sedimentation rate (32) but as this is a constant finding the test seems comparatively valueless in the nephrotic syndrome No satisfactory explanation can be advanced for the increases in these plasma fractions At one time hypothyroidism was suspected as a contributory cause of the raised plasma cholesterol but the rise in the nephrotic syndrome greatly exceeds that usual in myxoedema and is not abolished by administration of thyroid, even in amounts sufficient to produce tachycardia, restlessness and sweating No other clinical correlation has been established and though some decline in level often accompanies clinical recovery it is very gradual, showing no immediate swing in concert with dietary intake or diuresis

An attempt has been made to see whether the serum of patients with uncomplicated nephrosis differs from that of patients with other types of proteinuria (31) The former tend to show a greater increase both in cholesterol and in α globulin for any given degree of hypoalbuminaemia than patients with subacute nephritis These on the other hand like patients with acute nephritis tend to have higher levels of γ globulin Again, perhaps tests with isotopes will help to establish the nature of the metabolic derangement concerned in raising these various plasma constituents So far Spector (68) studying total globulins as prepared by a salting out technic has found no evidence of either increase or decrease in synthesis as compared with normal Similarly London Sabella and Yamasaki (41) find no change in cholesterol synthesis though apparently some prolongation of half life indicating deficient utilization can be detected

DIFFERENTIAL PROTEIN CLEARANCES AS DIAGNOSTIC AID

As already mentioned, the clearance of each globulin fraction can usefully be expressed as a percentage of the albumin clearance. It has been demonstrated that these percentages differ in proteinuria of varying origin as shown in Table I

Although as yet the number of patients studied is small a definite

depletion in the plasma might be anticipated This is in fact found, for these proteins are reduced in nephrotic sera Furthermore the degree of depletion of these fractions is greater in the more severely affected patients with more proteinuria and hypoalbuminaemia

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in the plasma The clearances of dextran preparations varying only in molecular size was first reported by Brewer (10) who used rabbits for these experiments In brief the clearance of molecules up to about 10 000 in molecular weight was equal to that of creatinine (which appears to give a valid measure of the glomerular filtration rate for water in rabbits) But tests with fractions of molecular weights of 25 000 and 38 000 showed clearances of only about 20 per cent and 5 per cent of the creatinine clearance Dextran exceeding about 70 000 molecular weight normally does not pass into the urine Thus the relationship between the clearances and molecular weight was consistent with a sigmoid curve ranging from 100 per cent of the creatinine clearance below 10 000 molecular weight to zero above 70 000 molecular weight Many biological dimensions distributed in nearly normal fashion give rise to sigmoid relationships when summed effects are considered So if the glomerulus is envisaged as a kind of *sieve these results are explicable if all the holes or pores in the sieve* transmit molecules up to 10 000 molecular weight many somewhat larger transmit molecules of less than 20 000 while only a few of extreme size are capable of allowing the passage of very large molecules This concept of graded pore size is in line with the general biological property of variability of structure it was put forward as an alternative to the more classical view based on the behaviour of the kidney toward haemoglobin and serum albumin (3) which implied a uniform pore size in the glomerular membrane with a correspondingly sharp cut off between excretable and nonexcretable macromolecules

Independent work by Wallenius (75) on the excretion of dextran confirms and considerably extends Brewers work, not only by a greater volume of work, a very careful preparation and analysis of dextran fractions and the use of two other species (dogs and man) but also by the testing of patients with proteinuria These patients it was found passed larger dextran molecules into the urine than normal persons—apparently the first unequivocal proof of the increased glomerular permeability which has been so long suspected to be a basis of proteinuria Wallenius also discussed in detail various alternatives to the graded pore theory of glomerular filtration It is possible that selective ultrafiltration might occur even with uniform pores through which the passage of the more closely fitting macromolecules was slowed Alternatively diffusion has been suggested (15) as the

pattern emerges In the *nephrotic syndrome* the clearances of the larger globulins relative to albumin are low In acute nephritis on the other hand during the stage when gross haematuria is detectable by naked eye examination comparatively little difference between albumin and globulin clearances is apparent In subacute nephritis with persistent microscopic haematuria an intermediate state of affairs is found These differences in pattern if confirmed may be of assistance

TABLE 1 —Pattern of Proteinuria in Renal Disease*

Diagnosis	Globulin Clearances (expressed as % of albumin clearances)			
	α_1	α	β	γ
Nephrotic syndrome				
Uncomplicated (7)	142 (75–239)	12 (3–25)	24 (6–50)	26 (2–46)
Complicated by cardiac failure or renal vein thrombosis (9)	115 (65–300)	15 (1–33)	30 (2–83)	29 (3–130)
Acute nephritis (2)	135 (100–150)	53 (26–100)	106 (58–160)	91 (10 82)
Subacute nephritis (4)	85 (32–195)	20 (0–41)	42 (10–68)	33 (7–71)

* Abridged from Hardwicke (29)
Figures are means in every case (range of observations in parentheses) Numerals in parentheses under diagnosis indicate number of patients studied, several tests (4 hour clearances) having been carried out on each patient.

in diagnosing doubtful cases At any rate they lead to a consideration of the nature of the renal damage found in these various conditions The coincidence between the larger molecular size e g of α globulin and the partial exclusion of these globulins from the urine at once suggests the analogy of the sieve—and in gross structural disease e g acute nephritis of a damaged sieve with abnormally large holes

SIEVELIKE BEHAVIOUR OF GLOMERULUS

As will be seen below proteins must now be regarded as subject to reabsorption by the renal tubules This imposes some limitation on using their behaviour to draw inferences about the state of the glomerular membrane But reabsorption apparently does not occur to any serious extent with the foreign macromolecule dextran since the clearance of this substance is unaffected by changing its concentration

plasma reaches a certain threshold value Above this level, an approximately linear relation exists between the amount excreted in unit time and the plasma concentration (24) This kind of relationship is characteristic of substances liable to tubular reabsorption it is generally believed that at threshold plasma levels these substances are being reabsorbed at the maximal rate of which the tubule cells are capable At higher plasma levels this maximal reabsorption continues but the excessive quantity in the glomerular filtrate leads to its escape into the urine The simple mathematical formulation of this idea is given in many accounts and in the review cited (59)

In patients with normal kidneys protein in excess of the usual trace amounts appears in the urine when the plasma albumin is raised by infusion to levels greater than about 5 5 Gm per 100 ml (18) With plasma albumin levels of between 6 3 and 6 9 Gm per 100 ml of blood a proteinuria of between 0 05 and 0 12 Gm per kilogram per day has been observed (35) There is no evidence that this proteinuria is due to renal damage and it disappears promptly when the serum albumin falls back to normal In other words the normal kidney of man appears to have a definite threshold for albumin Various reports show that in nephrotic patients albumin infusion leads to an increase in the loss of albumin per minute for as long as the serum level is raised above preinfusion level (2 16) In most instances graphical display showing the relation between the rate of albumin loss and the serum albumin level indicates a roughly linear relationship but so far the investigators have not felt that definite conclusions could be drawn from these results In part no doubt this has been due to technical considerations—until paper electrophoresis had been sufficiently developed repeated accurate measurements of albumin concentrations in serum and urine were difficult Yet the complete analysis of these variations in proteinuria in relation to changes in serum protein level is potentially of great importance for two properties—the glomerular permeability to various protein molecules and the maximal rate of tubular reabsorption—can theoretically be derived from it

Hardwicke (29) has now studied the results of albumin infusions (6 in all) in 4 patients with the nephrotic syndrome In each case nearly 50 Gm of 96 per cent pure human serum albumin was infused leading to a definite increase in the patient s serum albumin level for about 36 hours Clearance studies were carried out over 4 hour or 8 hour periods before and throughout this period until preinfusion levels were restored Creatinine clearances were estimated for each

major factor in the transmission of macromolecules such as protein, through the glomerular wall and this is also a selective process dependent upon molecular weight Wallenius is cautious in making a choice between these theories some calculations by Govaerts and Lambert (24) stress the need to consider diffusion seriously But it is difficult to see how diffusion could lead to the apparent identity between the clearance of molecules ranging between say 200 and 10 000 molecular weight while on the other hand the uniform pore theory may be thought not to account satisfactorily for the graded transmission found in the wide range between 10 000 and 50 000 molecular weight For the present the graded pore theory seems most readily to account for the known facts, and may be adopted as a useful frame work within which to classify experimental and clinical findings A tentative diagram has even been given (70) illustrating this view of the normal glomerular membrane and of changes which could account for the varying clearance patterns in acute nephritis and in the nephrotic syndrome

TUBULAR REABSORPTION OF PROTEIN

It is now widely accepted that tubular reabsorption of protein occurs, the evidence has recently been well reviewed by Rather (59) who has himself contributed experimental results Two lines of evidence support the reabsorption hypothesis the first is concerned with the histological appearances of the tubules especially when reabsorbing proteins which are coloured or can readily be stained (e g haemoglobin Evans blue [T 1824] bound by albumin fluorescent proteins) In this way the material selected is found at suitable intervals after its introduction into the blood stream lying apparently associated with the mitochondria in the cells of the proximal convoluted tubules Brewer (11) has recently made detailed studies of the brush border of these cells in rats injected intraperitoneally with haemoglobin haemoglobin filled spaces could be seen running across the border from tubular lumen into the cells At postmortem examination or after biopsy of nephrotic kidneys these tubular cells are usually loaded with fat and cholesterol More definite evidence of tubular damage in association with proteinuria is found in various kinds of poisoning especially with heavy metals The other kind of evidence for tubular reabsorption of protein as a normal function of the kidney is derived from clearance measurements of various proteins but especially of haemoglobin This protein is not found in the urine until its level in the

terms of the pore theory the percentage of glomerular pores passing albumin (molecular weight ≏ 70 000) can be found undistorted by the factor of tubular reabsorption which is eliminated by this method of calculation In the patient cited (C J a 54 kg girl) 1 1 per cent of the glomerular pores transmitted albumin The diagnosis in this patient was subacute nephritis and the globulin clearances fell within the range shown in Table I As the α globulin clearance for example was 20 per cent of the albumin clearance $1\,1 \times \frac{20}{100}$ or 0 2 per cent of the glomerular pores were sufficiently enlarged to transmit this large globulin a finding consistent with the microscopic haematuria which was also observed

Returning to the method of plotting already given it was shown that by extrapolation the total protein reabsorbed by the tubules each minute could also be calculated in the case of C J it amounted to 11 mg per minute or 15 Gm per day This slightly exceeded the level of protein escaping into the urine before albumin infusion so that over half of the protein passing into the glomerular filtrate was being reabsorbed Even this level of reabsorption is apparently well below the capacity of a normal kidney

This principle of calculating tubular reabsorption has been previously applied to other situations e g reabsorption of glucose (23 64) A possible criticism statistically is the lengthy extrapolation extending beyond the region of possible experimental verification e g below threshold values To meet this objection an alternative method of plotting and of calculating regressions may be proposed When

$$\left.\begin{array}{l} \dfrac{(\text{albumin clearance})}{(\text{creatinine clearance})} \\ \text{is plotted on the vertical axis against} \\ \dfrac{(\text{albumin clearance})}{(\text{creatinine clearance}) \times (\text{protein excreted/minute})} \end{array}\right\} \text{Method (2)}$$

a linear relation is once more obtained but the *slope* is in this case proportional to the rate of tubular reabsorption of total protein No extrapolation is therefore involved In theory the intercept on the vertical axis now corresponds to the rate of passage of albumin through the glomerular membrane relative to creatinine i e to the factor derived from the slope of plotting by Method (1)

Another difficulty concerns the introduction of the creatinine clearance into these calculations Quite apart from the question whether with suitable methods of estimation this is a satisfactory measure of

period similarly the clearances of albumin and of each of the four globulins separable by electrophoresis were calculated from measurements of serum and urine levels and of urine volume During the initial analysis of these results, albumin excreted per milliliter of glomerular filtrate was plotted against serum albumin level in a fashion exactly analogous to the method described by earlier workers studying haemoglobin excretion But when the globulin clearances were examined unexpected results were found Although the serum levels of the globulins were substantially unaffected by the albumin infusion, the clearance of each fraction rose in direct proportion to the albumin clearance When the serum albumin level and the albumin clearance fell back to preinfusion levels the globulin clearances also fell in the same way (33) This result seems explicable only if it is postulated that the tubular reabsorptive mechanism for protein is nonselective as between different serum protein fractions Presented with a protein loaded glomerular filtrate the tubule cells reabsorb protein at their maximal rate The relative amount of albumin and of each globulin reabsorbed is determined only by the relative concentration of each in the filtrate This in turn is affected by the glomerular permeability (assumed to remain unaltered during the short period covered by the clearance studies) and by the serum levels of each fraction

In the light of these findings the constant tubular reabsorptive capacity is thought to be concerned not solely with albumin but with total protein The simple plot between excretion and serum albumin level is therefore invalid to the extent that the preparation of albumin in the glomerular filtrate varies somewhat with changing serum albumin level and a perfect linear relationship is not to be expected The fully linear relationship should be between

$$\left.\begin{array}{c}\text{(total protein excreted/minute)}\\ \text{and}\\ \dfrac{\text{(total protein excreted/minute)} \times \text{(creatinine clearance)}}{\text{(albumin clearance)}}\end{array}\right\} \text{Method (1)}$$

The results of plotting in this way the findings after albumin infusion have been published (70) and the derivation of the expression given These results lie within the limits of current experimental errors on a straight line as demanded by the theory It is shown that the gradient of this line corresponds to the rate of passage of albumin through the glomerular membrane relative to creatinine This measurement defines to a large extent the degree of glomerular damage in any patient In

from these organs estimated Albumin reabsorption was estimated by comparing the results with the mean blood level of the dye in the hours before the animals death The calculations suggest that a minimum of one third of the circulating plasma protein was passing through the process of tubular reabsorption each day

Spector (69) has carried out similar studies using homologous proteins (serum albumin, γ globulin and haemoglobin) labeled with I^{131} Normal rats and others with nephritis induced by the injection of anti rat kidney serum were used Evidence of tubular reabsorption in both groups of animals was obtained quantitative measurements of radioactive protein in kidney cells and mitochondria were made and the site of the radioactive protein within the glomerular space and convoluted tubule cells was demonstrated by autoradiographs The quantitative results showed that with administration of similar quantities of the different proteins to different animals more haemoglobin, and less γ globulin, than albumin was reabsorbed This order is in accordance with the molecular weights of these proteins The animals with kidneys damaged by antiserum and passing much protein in the urine reabsorbed more of each protein than the normal animals In this kind of experimental renal damage therefore an increase in glomerular permeability is regarded as the main defect, it does not follow of course that in nephrotic patients proteinuria is determined by a similar mechanism

OTHER FORMS OF TUBULAR DYSFUNCTION

Electrolyte disorders are absent in most patients with the nephrotic syndrome Sodium, potassium, and chloride levels in the serum for example, remain constant for long periods in spite of the severe salt restriction often used in therapy Considerable tubular activity is involved in this homeostasis since urinary losses of sodium and of chloride may be less than 10 mEq daily for prolonged periods Occasionally a patient apparently cannot tolerate such severe salt restriction without a fall in serum electrolytes and perhaps also a rise in blood urea, changes which can be reversed by administration of sodium chloride (though this may then lead to further *oedema formation*) But, usually, the tubules of nephrotic patients are well able to perform the function of electrolyte control.

Some degree of tubular defect, however can be found in many nephrotic patients by the use of chromatography By this method the

glomerular filtration rate the uncertainty persists which of two quantities is really constant—the total protein reabsorbed per minute or the *total protein reabsorbed* per milliliter of glomerular filtrate *Although* the former seems more likely in theory, the matter is not readily tested since large variations in glomerular filtration rate do not seem to occur with the small albumin infusions given in these tests As pointed out by Homer Smith (67) as a practical expedient it is often useful to treat the reabsorption per milliliter of filtrate as constant, for this eliminates minor errors from the timing of urine collections or from incomplete bladder emptying (64) When this is to be done Method (1) should be plotted as

$$\left.\begin{array}{l} \dfrac{(\text{total protein excreted/minute})}{(\text{creatinine clearance})} \\ \text{against} \\ \dfrac{(\text{total protein excreted/minute})}{(\text{albumin clearance})} \end{array}\right\} \text{Method (1a)}$$

On the same basis Method (2) should be plotted as

$$\left.\begin{array}{l} \dfrac{(\text{albumin clearance})}{(\text{creatinine clearance})} \\ \text{against} \\ \dfrac{(\text{albumin clearance})}{(\text{total protein excreted/minute})} \end{array}\right\} \text{Method (2a)}$$

Provided that further trials substantiate these findings it would seem that the way is now open to the individual assessment of each patient with proteinuria at various stages of disease in terms of functional abnormality of glomerular membrane and of tubule As both factors have been shown to be affected in nephrotic patients though in varying degrees this assessment is worth while The procedures involved albumin infusion with repeated clearance measurements if carried out with due care are regarded as being as safe as most routine diagnostic procedures In the normal kidney from the findings quoted above for the threshold and rate of loss of protein at high serum levels active reabsorption of protein apparently proceeds at a considerable rate it has been suggested (29) that about 0 5 mg per milliliter glomerular filtrate is reabsorbed equivalent in normal subjects to about 85 Gm albumin per day Recently Sellers and others (63) have carried out tests in rats the serum albumin being dyed by injections of T 1824 At suitable intervals the animals were killed the kidneys perfused to remove blood and the content of dye extracted

During the last 30 years the plasma volumes of nephrotic patients have been measured many times mainly by administration of the dye T 1824 (34 71) As already noted this dye being rapidly linked to plasma proteins preferentially to albumin is lost into the urine when proteinuria is present This results in an abnormally rapid fall in plasma concentration so that unusual care is needed to deduce the plasma volume from estimations made at varying intervals after dye injection Furthermore the cloudiness of the lipid laden plasma of nephrotic patients introduces special problems in relation to the optical measurement of dye concentration Despite these technical difficulties it is now generally agreed that the plasma volume is reduced in the nephrotic syndrome the circulating red cell mass is then usually also subnormal when calculated from the corresponding haematocrit measurement Occasionally when oedema has developed rapidly the haematocrit value is raised above 45 per cent, indicating that the plasma volume was reduced before true anaemia (i e reduction of circulating red cell mass) developed In nephrotic patients with low haematocrit levels the plasma volume may be normal in the sense that it equals the accepted value of 45 ml per kilogram body weight for persons without anaemia But it is now known that in simple anaemia the plasma volume is ordinarily raised (51) In short, during the phase of oedema and prior to the onset of diuresis the total blood volume of nephrotic patients is probably always reduced when compared with the normal or with patients suffering from a corresponding degree of simple anaemia This appears to be an essential feature of the syndrome further studies are needed particularly of simultaneous direct estimation of plasma volume (e g by infusion of labeled protein) and of circulating red cell mass (e g with labeled erythrocytes)

The reduction of the blood volume is usually of the order of 20 to 30 per cent More severe reduction would presumably render the patient prone to some form of circulatory failure such as a general shocklike state or a local failure to maintain an adequate blood flow to some organ It is possible that some of the pallor of nephrotic patients depends on a compensatory constriction of skin capillaries Definite circulatory failure is not a feature of the syndrome although severely affected patients are certainly more comfortable when at rest in bed With some forms of treatment such as severe and prolonged salt restriction the withdrawal of salt by resins or enforced urinary loss by mercurial diuretics, nephrotic patients may complain of addi

presence of glucose is revealed in a number of patients although the conventional tests (e g with Benedict s reagent) fail to give unequivocal results in the presence of heavy proteinuria The glycosuria is found during periods when the blood sugar level is within the normal range, so that tubular dysfunction can be presumed Aminoaciduria has also been reported by Milhaud and Courvoisier (50) and by Blainey (5) a considerable variety of amino acids being found including many not present in normal urine Plasma levels of individual amino acids have not been sufficiently studied as yet but the over all level is not raised Again therefore tubular dysfunction is thought to be responsible for this wastage into the urine Glycosuria and aminoaciduria have been shown by Lowe and associates (43) to occur in the recovery phase after acute tubular necrosis and in a number of other renal disorders no glycosuria was found in the nephrotic patient included in this series Both abnormalities are found in chronic poisoning of the kidney e g by lead and by uranium

Occasionally aminoaciduria in the nephrotic syndrome may be so pronounced as to be of interest not only in relation to renal tubular function but also in terms of its effect on nitrogen balance The loss of nitrogen in this form may be comparable to that lost in the form of protein constituting an additional reason for adequate dietary therapy (5) The urinary loss of amino acids may also perhaps contribute to the nephrotic crisis described by Farr and MacFayden (20) These attacks found to be accompanied by very low plasma levels of amino acids were reported before chromatography was available, and could now be even more fully investigated

BLOOD VOLUME CHANGES

In 1924 Linder Lundsgaard van Slyke and Stillman (38) showed by the methods then available that the blood volume was not increased in the nephrotic syndrome This finding was of fundamental importance in discounting the idea that the basis of the hypoproteinaemia of the low haemoglobin level and of the oedema was simply an inability of the kidney to excrete water Contrariwise this state of affairs is now recognized as operative in the anuric phases of acute tubular necrosis and of acute glomerulonephritis in which haemodilution and oedema can readily be aggravated by allowing the patient to drink more water than he can lose

expected as the time needed for internal adjustments by transfer of fluid between different bodily compartments though short, is appreciable

The implications of these measurements on plasma volume changes should not be overlooked when considering the correct dosage of any colloid infusion which is to be given to a nephrotic patient In a patient with a plasma colloid osmotic pressure of say one third normal any colloid infused would have a three times greater expanding effect on the plasma volume than the same dose in a person with normal plasma if full expansion occurred in both instances in iso osmotic fashion It follows that cautious dosage and slow rates of administration are indicated in nephrotic patients for although completely iso osmotic expansion does not occur and although the plasma volume before infusion tends to be low in nephrotic patients circulatory overloading with congestion of the neck veins is sometimes seen with this form of treatment With 900 ml of a 6 per cent dextran solution given over a period of 12 hours for example a 50 kg female patient showed an appreciable rise in venous pressure

The relation between blood volume and the excretion of salt and water may be the immediate determining factor between oedema formation and diuresis Before the onset of spontaneous diuresis a fall in haematocrit may be observed (70) These effects are gradual as shown especially by daily measurements of chloride loss on a steady salt intake after weeks or months of strict chloride conservation by the kidney the amounts lost creep up somewhat irregularly day by day until the chloride output exceeds the intake and the dramatic losses associated with a massive diuresis appear But the kidney is also capable of acute change from conservation to elimination of chloride not only under the influence of mercurial diuretics but also after the infusion of salt free colloids such as albumin or dextran After infusions of colloid equivalent to 50 Gm of albumin an immediate transient diuresis of water and chloride is usually seen after 24 to 48 hours the effect is over but can be obtained again and again by further infusions Occasionally a single infusion of albumin dextran blood or other colloid is associated with the onset of a continuing diuresis in these circumstances it may be considered that a spontaneous diuresis had been near The similarity between the diuresis period and the time during which the blood volume is expanded after these infusions supports the idea that the kidney responds to a normal blood volume by chloride release conversely the salt retention observed

tional symptoms such as headache or weakness and increases in blood urea may be observed, possibly attributable to a fall in renal blood flow below a critical level

Orthochromic normocytic anaemia is in general not well understood the anaemia of this type found in nephrotic patients is no exception Careful tests of the *survival of infused red cells* distinguishable from those of the patient have been carried out in patients with various kinds of renal disease (13) In those with advancing renal lesions a shortening of red cell life to about 60 or 40 days was found In other patients not deteriorating the transfused cells survived normally so that the anaemia was presumably due solely to underproduction of erythrocytes This factor also seemed to be operative in some of the patients showing some abnormal destruction of infused cells These results are in essential agreement with other reports (40) and with clinical experience of the results of therapeutic blood transfusions Transfusion appears to benefit nephrotic patients who are anaemic but the anaemia recurs in about 6 to 8 weeks so that repeated administration of blood may be needed over long periods

The dual abnormality in the plasma—reduced volume and reduced albumin concentration—presents an interesting question If albumin is infused which abnormality will be corrected more? As pointed out by Chinard and co workers (17) either the colloid osmotic pressure of the plasma might remain steady (iso osmotic), so that volume correction occurred, or the volume might stay constant at its reduced level (isometric), thus allowing the increase in circulating albumin to raise the colloid osmotic pressure potential of the plasma In fact, in a series of test infusions, an intermediate effect resulted, both the plasma volume and colloid osmotic pressure (calculated from protein concentrations) tending to rise somewhat In unpublished observations we have confirmed these findings although an additional factor the time sequence of the effects needs to be considered When an infusion of concentrated albumin (e g 10 20 Gm per 100 ml) is administered to an oedematous patient the plasma concentration tends to be raised *in the first few hours Later plasma volume expansion* (as judged by a fall in haematocrit) ensues Thereafter albumin is lost from the circulation partly into the urine and partly elsewhere this causes a fall in plasma protein concentration and so presumably in colloid osmotic pressure Finally the plasma volume contracts once more approximately to preinfusion levels the whole sequence of events being complete in *36 to 48 hours This kind of hysteresis effect* is not un

expected as the time needed for internal adjustments by transfer of fluid between different bodily compartments though short, is appreciable

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during oedema formation may be regarded as a physiological response to a reduced blood volume These ideas are in line with those put forward by Borst (8) In any case there seems no doubt that the nephrotic kidney is at all times well able to excrete salt, given the appropriate stimulus In this account emphasis has been laid on salt (sodium and chloride) as the main variable in determining renal control of the body's fluid content Salt free water can be eliminated by the nephrotic patient even when the daily intake is increased by 1 to 2 litres It is true that some abnormal delay in water elimination is usual but this may be attributed to the great increase in the total body fluid throughout which the water drunk can be distributed

The controlling factor guiding the kidney's behaviour in conserving or eliminating salt is probably a hormone Until recently it was felt that a hormone derived from the posterior pituitary might be concerned although in general this gland is active in ensuring rapid adjustments of water balance rather than in controlling the salt content of the body Attention is now focused on the adrenal cortex and especially on the discovery by Simpson and Tait (65) of a natural salt retaining hormone (electrocortin aldosterone) The chromatographic separation of a sodium retaining corticoid from the urine of children with nephrosis by Luetscher and Johnson (45) seems to offer a clear explanation of the salt retention found not only in nephrosis but also during oedema formation in other conditions such as cardiac failure Separation of the hormone was effected on filter paper the positions of various steroid bands being evident on examination in ultraviolet light Sufficient quantities could be eluted from the appropriate parts of the paper strip to test their properties when injected into small animals Control tests proved the absence of this hormone from the urine of normal children Nevertheless the secretion of salt retaining hormones is to be regarded as a physiological adjusting mechanism brought into play when necessary Further work on this important development may enable the clinician to watch the progress of individual patients with nephrosis and to elucidate with more certainty the mechanism of diuresis following colloid infusion

MECHANISM OF OEDEMA FORMATION

The Starling hypothesis must still be the starting point for discussing oedema formation the main complaint of the nephrotic patient Figure 3 attempts to integrate the preceding sections with this theory

Though consistent with most of the known facts this supposed sequence of events is not firmly enough based on repeated accurate measurements to be regarded as fully proved Certainly it omits many important undiscovered effects The scheme even contains logical diffi

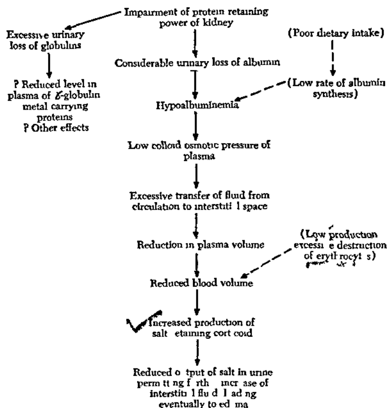


FIG 3—Theory of sequence of events in nephrotic syndrome Parentheses dotted lines indicate complications often present but not essential features of the syndrome

culties as for instance in understanding how a patient once oedema formation has commenced does not proceed to transfer very much more of the plasma ultrafiltrate into the interstitial space

As the oedema fluid in the nephrotic syndrome has a very low protein content it is usually assumed that abnormal permeability of capillary walls to colloids is not a factor in nephrotic oedema A lowered plasma colloid osmotic pressure is therefore regarded as the abnor

during oedema formation may be regarded as a physiological response to a reduced blood volume These ideas are in line with those put forward by Borst (8) In any case there seems no doubt that the nephrotic kidney is at all times well able to excrete salt given the appropriate stimulus In this account emphasis has been laid on salt (sodium and chloride) as the main variable in determining renal control of the body's fluid content Salt free water can be eliminated by the nephrotic patient even when the daily intake is increased by 1 to 2 litres It is true that some abnormal delay in water elimination is usual but this may be attributed to the great increase in the total body fluid throughout which the water drunk can be distributed

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MECHANISM OF OEDEMA FORMATION

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Oedema is not usual with only moderate lowering of serum colloid osmotic pressure to levels which are not below 20 cm water This does not necessarily mean that small increases in interstitial fluid volume may not be present, as oedema is not detectable until the whole limb has increased 5 to 10 per cent in volume or the interstitial fluid is increased by 20 to 40 per cent Nevertheless some active readjustments must be called into play to compensate for a plasma colloid osmotic pressure of less than half the normal value It is natural to consider reductions in capillary blood pressure and increased lymphatic drainage as being possible reactions tending to prevent oedema formation. Very few measurements have yet been made on nephrotic patients to find such alterations but the experiments of Smirk (66) are certainly worthy of repetition After determining plasma colloid osmotic pressure in normal subjects and in patients with renal or hepatic disease a congesting cuff was fixed on the upper arm and inflated sufficiently to raise capillary pressure to a constant amount above the colloid osmotic pressure Measurements were then made of the rate of swelling of the limb It was concluded that in patients suffering from nephritis at various stages in the disease including one example of the nephrotic syndrome increased swelling occurred under these standardized conditions These findings seem to conflict with the belief that capillary permeability is normal in nephrotic patients

Another extension of the Starling hypothesis may be needed when the physical state of the interstitial fluid is more thoroughly known When the hypothesis was first put forward in 1896 it had not been shown that this volume was normally about five times larger than the plasma volume Oedema was probably considered to be due like ascites or pleural effusions to the presence of fluid in places where very little was normally to be found In fact oedema fluid behaves in ways which differ from those of normal interstitial fluid it moves from place to place under the influence of gravity or pressure and it can readily be removed from the body through a needle or skin incision These qualitative differences suggest that normal interstitial fluid does not consist of free water but is bound like the water in 5 per cent gelatin to a hydrophilic gel Such an idea can be linked to the concept of an interstitial ground substance which has been described in terms of its ability to take up various stains (22) It has also been shown in experiments that interstitial substances can swell in water or in saline to a varying extent depending on the tissue from which it is derived (57) This swelling may correspond with the increase in limb volume

mality explaining nephrotic oedema in terms of the Starling theory It is generally agreed that a low plasma colloid osmotic pressure is found in the syndrome but many more measurements are needed to assess the exact level which leads to oedema in patients who differ in salt intake age, physical activity and other respects Until recently the measurement of colloid osmotic pressure has been difficult Rapid accurate results are now obtainable with Rowe's osmometer (61), which uses a simple electronic device to discover the hydrostatic pressure which has to be applied to a plasma specimen exactly to balance the colloid osmotic effect across a semipermeable intracellular membrane Doubt has recently been cast (1) on the accepted idea that plasma protein concentration alone determines colloid osmotic pressure and this work needs careful consideration Certainly simple calculations even from a full electrophoretic analysis of the different plasma protein levels are not enough to give more than an approximate estimate of the corresponding colloid osmotic pressure For even at the reduced concentrations found in nephrotic plasma colloid osmotic pressure does not obey the simple gas laws predicting a linear dependence on concentration Instead colloid osmotic pressure tends to rise more steeply with concentration at physiological levels of the plasma proteins than are found in very dilute solutions this would be expected by the physical chemist for such a system contains moderate concentrations of charged molecules which also are probably capable of binding appreciable amounts of water Experimental demonstration of this curvilinear relationship was obtained in 1926 by Mayrs (49) It has recently been suggested that the steep increase in colloid osmotic pressure with plasma protein concentration at normal levels is of physiological importance in helping to ensure accurate homeostatic control of plasma volume (70) This effect is lost to a considerable extent at the reduced levels found in nephrotic serum so that for this reason alone the volume of both plasma and interstitial fluid can be less accurately regulated in these patients

As noted in Figure 2 the presence or absence of oedema is largely dependent on serum albumin concentration Below 1 Gm per 100 ml oedema is usual while at concentrations between 1 and 2 Gm per 100 ml oedema can usually be controlled especially by low salt intake or salt depleting therapy Closer dependence on colloid osmotic pressure would be anticipated in fact in our experience nephrotic oedema is usually present with serum colloid osmotic pressures below 15 cm water and may be present with pressures below 20 cm water

ble as oedema would be present On the other hand in dehydrated states the reduced water content of the interstitial spaces correspond to a rise in imbibition pressure In such a system the imbibition pressure of the normal interstitial substance would act in the opposite sense to the larger colloid osmotic pressure of the plasma The constancy of the interstitial fluid volume would then normally depend not only on the change in colloid osmotic pressure with plasma protein concentration but also on the change in imbibition pressure of the interstitial gel with variations in the water content of this space These possible relations have been expressed in graphical form (70) as shown in Figure 4

This hypothesis needs to be tested experimentally An instrument has now been made which has proved satisfactory for measuring the small imbibition pressures of gelatin in well hydrated gels containing 90 to 96 per cent water (62) Contact is made between saline and the gelatin through the porous sintered metal wall of a hollow needle attached to a manometer system Movement of very small amounts of fluid through the needle s wall is detected by an electronic system analogous to that used in Rowe s osmometer (61) The negative pressure required to prevent imbibition can be accurately determined in centimeters of water The needle has been designed for introduction beneath the skin but insufficient trials have as yet been made to be sure that an appreciable imbibition pressure is in fact characteristic of the normal interstitial tissues

EFFECT OF VARYING PROTEIN INTAKE ON *NITROGEN BALANCE*

Although the continuing large urinary loss of protein is the main cause of hypoalbuminaemia deficient production of albumin may be a contributory factor in nephrotic patients given an inadequate diet This leads to the question of what constitutes an adequate and what an optimal diet, for the nephrotic patient At present, there is general agreement that low protein diets are not indicated but there is less certainty whether these patients benefit more from an ordinary level of intake or from high protein diets The criteria on which a decision can be taken are therefore worthy of consideration Clinical recovery must be the final object, and a reversion of the serum chemistry toward normal such as a rise in the circulating serum albumin may be accepted as an index of progress But the clinical course of the syndrome

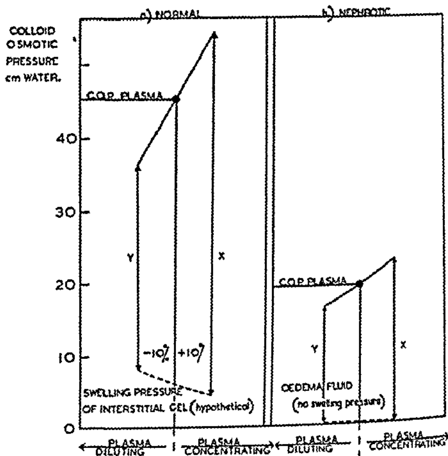


Fig 4—Changes in volume due to transfer of ultrafiltrate between plasma and interstitial space may be minimized not only by ensuing changes in colloid osmotic pressure (C O P) of plasma but also by postulated changes in swelling (imbibition) pressure of the interstitial gel. Efficiency of controls in normal subjects (a) is indicated by the difference (X–Y) it is probably much less in the nephrotic patient (b) as shown by the smaller difference (X_1–Y) (70 reproduced by permission of the editor British Medical Journal)

which must occur before oedema is found But hydrophilic gels exert an appreciable imbibition pressure sometimes known as a swelling pressure (56) which diminishes as their water content is increased It would be expected therefore that normal interstitial substance would exert an imbibition pressure which would fall with increasing water content until a point was reached at which no further fluid could be bound with further addition of water free fluid clinically recogniza

protein supplement These results are derived from over all protein balances sometimes called assimilated retained nitrogen no allowance being made for protein lost in the urine which was included along with urinary nonprotein nitrogen and faecal nitrogen in the debit column of the balance sheets

Another indication of the beneficial results of high protein feeding in these patients was given by the large cumulative positive nitrogen balances which were obtained A gain of 312 Gm nitrogen over a period of 48 days was recorded in the 72 year old man of 85 Kg standard body weight the 20 year old girl weight 55 Kg gained even more—488 Gm in 99 days Assuming 1 Gm of nitrogen to correspond with 6 25 Gm of protein this is equivalent to about 3 Kg of dry protein a considerable gain Daily weighings were made throughout the period and from these it was possible to see whether the retained nitrogen was being used for cellular repletion, in other words whether the patient was literally putting on flesh During the earlier part of the study there was a considerable diuresis accompanied by a gross loss in weight later when the net chloride balance was zero for several weeks showing that no further loss or gain of oedema occurred there was a steady weight gain in each period proportional to the nitrogen gain For every gram of nitrogen retained there was about a 25 Gm weight gain If then each gram of nitrogen was being converted to 6 25 Gm of protein this protein was associated with three times its own weight of water As intracellular substance is considered to be about 30 per cent protein and 70 per cent water while the extracellular compartments contain much more water this patient could be regarded as using most of the assimilated and retained nitrogen for repletion of cellular protein At the start of the tests the deficiency which was subsequently restored must have amounted to about one fifth of the total protein normally contained in her body

The benefit derived from the periods of high protein feeding seems to be clear but useful information was also derived from calculating the diet necessary for each patient to remain in equilibrium with neither a net gain or loss of nitrogen In the two adult patients the intake corresponding to zero nitrogen balance was between 0 14 and 0.20 Gm nitrogen per kilogram per day equivalent to protein intakes of 60 to 90 Gm protein daily in a 70 Kg adult In the third patient studied a girl of 14 in the course of normal puberal development the corresponding intake amounted to 0 37 Gm per kilogram per day On lower intakes these patients could be expected to be in negative

is known to be variable particularly in duration Improvement is usually slow on any diet and without a large series of patients divided into groups given different diets an unequivocal answer cannot be given on this basis Changes in the daily loss of protein in the urine are unacceptable unless considered in relation to serum albumin level, for as already pointed out small rises in serum albumin concentration which probably represent a clinical improvement may be accompanied by increased protein loss For the assessment of progress in comparatively short term clinical trials changes in nitrogen balance are probably the most satisfactory index

It is now well known that normal adults remain approximately in zero balance showing neither a net gain nor loss of nitrogen even on considerably different protein intakes When the intake is abruptly increased a positive balance is found for a few days but very soon urea excretion rises to match the extra intake On the other hand a reduction to low intake such as 30 Gm of protein daily in an adult, results only transiently in a negative balance after which equilibrium is once more restored provided that the quality of the restricted protein intake is satisfactory This implies of course that the normal subject can reduce the urinary loss of nitrogen to a correspondingly low level e g to 0 05 Gm nitrogen per kilogram body weight daily

Recently Blainey (5) has carried out prolonged nitrogen balance studies on 3 nephrotic patients aged 14 20 and 72 years The dietary intake was varied at different times between 60 and 180 Gm (occasionally even up to 200 Gm) protein per day and sufficient data were therefore obtained for the results to be analyzed statistically A straight line relationship was found between protein balance and protein intake with no indication of any tendency for the extra dietary protein even at the highest levels to fail to increase the degree of positive balance still further From the slope of the line relating nitrogen balance to intake estimates could be made of the efficiency with which the protein supplements increased the nitrogen balance This was found to lie between 65 ±12 per cent and 78 ±17 per cent in other words the patients appeared to have no difficulty in assimilating and retaining within their bodies the nitrogenous constituents of the diet The diet was low in salt and of a normal mixed type including meat fish and eggs the supplements were mainly in the form of salt free milk powder and formed about 50 per cent of the total protein intake The efficiency of retention of about 70 per cent was therefore similar to that found in animal tests of the biological value of this kind of

may have been that Farr's patients were maintained on an approximately steady caloric intake so that when the protein intake was increased the carbohydrate was reduced Blainey was unable to maintain a steady caloric intake and during the periods of very high protein intake more fat and carbohydrate were also given It is worth noting that none of Farr's patients registered a gain in weight, despite an appreciable cumulative amount of assimilated retained nitrogen It is possible therefore that on higher caloric intakes nephrotic children might show an even more strongly positive nitrogen balance on daily intakes of 0 5 Gm nitrogen per kilogram body weight than on this level of intake This view receives some support from the work of Liu and Chu (39) who showed that increased caloric intake with a steady nitrogen intake could increase the nitrogen balance in nephrotic patients The classical studies of Peters and associates (58) emphasized the importance of the diet being well provided with both calories and proteins

It is clear that more trials are needed to establish the optimal diet for the nephrotic patient. For the present one may tentatively conclude that a high protein diet of not less than 120 Gm protein per day for a normal sized adult, containing not less than 2,800 calories daily seems best for promoting a state of positive nitrogen balance Larger intakes if tolerated without gastrointestinal upset, may lead to even more rapid repletion of severely depleted patients Unless special attention has been given to maintaining the intake of food in the face of a poor appetite the protein deficit of a nephrotic patient may be considerable after some months of illness Clinical evidence of response to the diet may therefore be slow to appear Periodic simple analyses (total protein and urea nitrogen) of 24 hour urine specimens considered in relation to the diet, give a valuable indication of the trend of the nitrogen balance since in the absence of diarrhoea faecal losses of nitrogen are usually only of the order of 2 Gm nitrogen daily in adults Whenever opportunity presents, 3 day balance periods on various levels of intake may be recorded, not only to decide the relative merits of different diets for the individual patient but to extend definite knowledge of the correct treatment for various types of nephrotic patients

Since the best level of over all protein intake remains to be established definitely it is not surprising that there is yet little knowledge guiding a choice of the best kind of protein By analogy with experiments on animals subjected to plasmapheresis animal proteins such

nitrogen balance though in fact only one of the patients was given a diet sufficiently restricted to induce negative balances for a time A study of the urinary nitrogen partition showed that the urinary protein loss in these patients was equivalent to between 0 02 and 0 06 Gm nitrogen per kilogram per day only, and at ordinary levels of protein intake the nonprotein nitrogen other than urea amounted only to 0 01 to 0 02 Gm nitrogen per kilogram per day It follows that even at the lowest levels of intake the urea loss amounted to 0 10 to 0 15 Gm nitrogen per kilogram per day—a figure which is appreciably greater than the urea losses of normal persons on very restricted protein intakes The adult nephrotic patient even to remain in zero nitrogen balance, evidently requires more than the normal minimum plus an allowance corresponding to the urinary loss of protein This finding is not unexpected since the amino acid composition of the serum proteins is somewhat specialized, and it is unlikely that ordinary dietary protein is so balanced as all to be capable of use with 100 per cent efficiency in plasma protein synthesis The nephrotic patient therefore sustains an obligatory loss not only of protein but also of urea which makes his minimal needs at zero balance greater than normal

These results have been given in some detail as they constitute the most recent study available The conclusions differ in some respects from the findings of similar careful tests carried out in 1938 by Farr (19) With increasing intakes over a range of 0 1 to 0 5 Gm nitrogen per kilogram ideal body weight Farr also found a steady increase in assimilated retained nitrogen But at higher intakes (0 6 to 0 8 Gm nitrogen per kilogram ideal body weight) the output of urinary non protein nitrogen was increased in every case to such an extent that the nitrogen balance became less positive than on intakes of 0 5 Gm nitrogen per kilogram weight Farr concluded that optimal results could be obtained not by giving very high protein diets but by maintaining a diet approximately normal in protein content

An apparent contradiction between two trials is usually due to different conditions Farr s 5 patients were 4 year old children while Blamey studied 2 adults and 1 adolescent Of Farr s patients 4 were oedema free at the time of the trial and all had been on a good measured dietary intake for some time beforehand whereas Blamey was studying oedematous patients who had not previously received such careful dietary treatment The main item used to increase the diet of Farr s patients was meat chiefly beef salt free milk powder made up the bulk of Blamey s supplement But the most significant difference

Bed rest, dietary requirements transfusion for anaemia salt limitation or depletion and even paracentesis for relief of extreme oedema seem at times to be of value in all types of nephrotic patients Transient relief only is to be expected from most forms of colloid infusion such as dextran or albumin and caution is needed to avoid overloading of the circulation The judicious use of chemotherapy to control intercurrent infections certainly improves prognosis The range of usefulness of hormonal therapy has not been included in this discussion as the effectiveness of adrenocorticoid therapy has been reported by various groups in North America

The use of the term "nephrotic syndrome introduces a danger if it is regarded in any way as a final diagnosis Even though symptomatic treatment may be instituted as soon as the syndrome is recognized the search for a diagnosis of a specific condition and when possible for a definite aetiological agent should be continued It must be conceded that, after separating clear cut examples of subacute glomerulonephritis a specific diagnosis can usually be assigned only to a minority of the remaining patients But every attempt should be made to increase this proportion The history should include enquiry about exposure to infective or toxic chemical agents (76) and drugs (52) There is some reason to believe that nephrosis in early syphilis and with some drugs as tridione represents an allergic or sensitization phenomenon Overexposure to therapeutic irradiation has caused various forms of nephritis (46) Useful diagnostic procedures include biochemical techniques for recognizing diabetes amyloid disease and other metabolic disorders while chemical tests are available for heavy metals and other poisonous substances The distinction between proteinuria arising equally or unequally from the two kidneys may be important (47 55) Special mention must be made of the increasing value of roentgenography particularly with the introduction of contrast media into the aorta above the level of the renal arteries (27 54) Two further examples of renal vein thrombosis have been recently described (6) and verbal communications about others have been received At the Postgraduate Medical School of London (72) contrast material has been introduced into the inferior vena cava and so by reflux after raising intrapulmonary pressure (Valsalva procedure) into the renal veins giving good roentgenographic definition Serological procedures at present serve to exclude syphilitic infection and other spirochaetal conditions in glomerulonephritis antistreptolysin titres and Griffith s typing of streptococci may be required

as meat or whole milk are preferable Animal serum has also been used Knowledge of the essential amino acid groupings is still too recent to have influenced greatly clinical methods of treatment As pointed out by Bradley and Tyson (9), special attention might be given to the extent of sulfur containing amino acids in the diet Simultaneous nitrogen and sulfur balances were carried out by Grabfield and Prescott (26) showing the course of events not only in nephrotic and cirrhotic patients in positive balance but also in patients with acute nephritis during periods of body depletion Surprisingly high sulfur nitrogen balance ratios were shown in every case These appear to be greater than the ratios of sulfur nitrogen content in the proteins of serum or muscle Perhaps the more labile substances requiring repletion in the nephrotic patient include mucoproteins of specialized cells or interstitial tissue Radioactive sulfur has also been used to study the formation of plasma protein and active incorporation was found (37) After standard dosage higher levels of radioactivity were found in each milliliter of nephrotic plasma than in normal controls These results may be compared with Spector s (68) findings using isotopic nitrogen In each case the admixture of normal amounts of newly formed plasma protein with a small body pool seems to account for high concentrations of isotope At any rate dietary sulfur can evidently be used for protein synthesis by the nephrotic patient in the normal way and an adequate intake of sulfur as well as of nitrogen is required Other essential groups such as labile methyl groups which are normally found in dietary amino acids and other substances may also be required in greater amounts than in the normal diet and isolated claims (7) have been made of dramatic clinical improvements following the administration of specific supplements e g of choline At present however it seems unlikely that a specific deficiency of this kind is likely to be a common factor in nephrotic patients

NEPHROTIC SYNDROME AN INCOMPLETE DIAGNOSIS

As stated in the introductory paragraph the use of the term "nephrotic syndrome is justified empirically since it can be employed to include a number of conditions in which a closely similar series of bodily changes can be found and interrelated In this review emphasis has been laid on these common changes and on the rational basis for symptomatic treatment as far as it is currently understood

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Useful information may on occasion be obtainable from renal biopsy (36) It is to be hoped that more extended use of these and of other improved methods will lead to accurate diagnosis and specific prophylaxis or treatment for the various conditions which give rise to the nephrotic syndrome

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Applied Pulmonary Physiology

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HISTORY AND TECHNICAL DEVELOPMENT

VENTILATORY FUNCTION TESTS —The study of the physiologic importance of the lung volumes and their measurement is an old chapter in pulmonary physiology Numerous investigators (21 48) have confirmed the fact that the total lung volume (Table 1) consists essentially of the vital capacity and the residual volume defined as the air remaining in the lung after a maximal expiration Clinical application of such knowledge was delayed by inability of investigators to develop simple and reproducible procedures for estimating the residual air Not until the early 1930's were modern technics evolved for residual air determinations based on the very simple principle of the measurement of the dilution of a physiologically inert gas of known concentration such as helium by closed circuit (rebreathing) methods (21) Later Darling and associates (31) developed an open circuit (non rebreathing) method, utilizing pure oxygen to wash out the nitrogen from the lung, and by the dilution of the nitrogen, calculating the volume of the residual air These methods permitted the statistical analysis of large numbers of patients and for the first time two simple clinical methods became available to investigators In this country the open circuit method is now commonly employed

The open circuit method of Darling and co-workers had the additional advantage of permitting measurement of the alveolar nitrogen

I wish to express my appreciation to the Medical Illustration Department of The Bronx Veterans Hospital for the preparation of the illustrations used in this paper

tive tracing of the maximal breathing capacity in pulmonary emphysema can be considered a hallmark of the disease (6) (Fig 1) It is the one simple laboratory test that helps to evaluate the integrity of chest wall lung tissue and the bronchial tree The concept of the lung

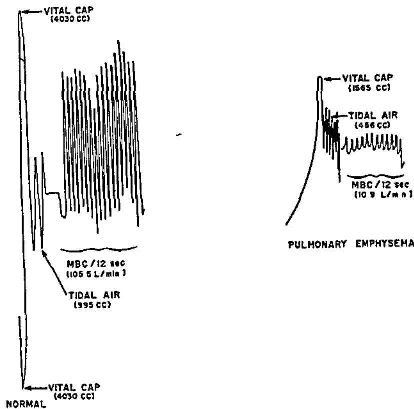


FIG 1—Normal and obstructive spirograms with maximal breathing capacity (MBC)

and its passages and the framework of the chest cage as a mechanical bellows system has largely developed from analysis of the obstructive tracings seen in the spirograms of emphysema cases (6) In our experience the appearance of a reduced maximal breathing capacity may be the earliest objective sign of ventilatory difficulty in patients who are otherwise asymptomatic The technics and applications of differential lung function study by means of bronchospirometry will not be

concentration remaining in the lung after 7 minutes of pure oxygen breathing This figure was shown to be a rough index of the efficiency of distribution of inspired gases to the alveoli A value greater than 2.5 per cent alveolar nitrogen could be correlated with those diseases characterized by impaired alveolar ventilation i e, emphysema (28) More precise methods for detecting uneven alveolar ventilation (26)

TABLE I.—LUNG VOLUMES VENTILATION AND OXYGEN CONSUMPTION
("NORMAL RANGES IN AN ADULT MALE HOSPITAL POPULATION)

I Lung volumes	
Vital capacity cc	3 800-5 000
Residual volume cc.	*1 000–1,300*
Total lung volume, cc.	4 500-6 000
Ratio of residual vol to total vol × 100	< 35
Index of intrapulmonary mixing nitrogen%	< 2 5
II Maximal breathing capacity (liters/min)	100–160
III Ventilation (liters/min /sq M of body surface area)	
Basal (rest)	3-4
Exercise (30 step for 1 min)	9–10
1st min. recovery postexercise	12
IV O_2 consumption (cc /min /sq M of body surface area)	
Basal (rest)	120-140
Exercise (30 step for 1 min)	400-550

* Unless noted all values are directly measured.

have been developed recently but the equipment required makes their routine use difficult and their clinical utility remains to be established In our hands the Darling method has been valuable and has correlated well with other laboratory signs of obstructive ventilatory insufficiency The figure of 2 5 per cent is somewhat high for normal subjects but as a maximum "normal figure does retain some clinical value

The concept of the maximum ventilation in liters per minute that an individual could produce was brought to its present form as the maximal breathing capacity Like so many of the technics developed to a point of clinical usefulness by the Cournand group it is a simple measurement which can be made on the ordinary spirometer It has proved to be a means of evaluating some of the gross mechanics of ventilation and of reflecting to a degree the over all resistance to air flow in the tracheobronchial tree (5) In this sense the characteristic "obstruc

tive" tracing of the maximal breathing capacity in pulmonary emphysema can be considered a hallmark of the disease (6) (Fig 1) It is the one simple laboratory test that helps to evaluate the integrity of chest wall lung tissue and the bronchial tree The concept of the lung

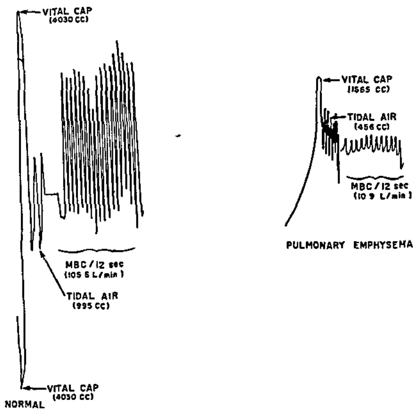


Fig 1—Normal and obstructive spirograms with maximal breathing capacity (MBC)

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discussed here A number of recent and excellent reviews on the subject are available (45 95)

The determination of oxygen consumption (Table 1) and total ventilation at rest and on exercise together with the determination of the total lung volume including residual air and the maximal breathing capacity comprise the usual and best known clinical tests of ventilatory function They have found widespread acceptance because of ease of performance and reproducibility of results These methods used in conjunction with arterial blood studies for oxygen and carbon dioxide content at rest and with exercise tended to separate abnormalities of pulmonary function into two groups *(1)* cases primarily with ventilatory difficulty and *(2)* cases with alveolorespiratory insufficiency In the latter group abnormal function results either from impairment of diffusion of gases across the alveolocapillary membrane and/or from poor distribution of gases to the alveoli (5)

The functional abnormalities of a disease state such as emphysema with anoxia and hypercapnia could then be related primarily to gas distribution and ventilatory difficulties Clinical states such as the interstitial fibroses of the lung characterized by anoxia without hypercapnia and with seemingly adequate ventilation (in fact hyperventilation) could be separated from the emphysema group and their pathophysiology established as due to processes causing impaired diffusion of gases between the pulmonary alveolus and capillary (7)

PULMONARY GAS EXCHANGE AND ITS MEASUREMENT —Extension of the evidence to separate gas exchange into a distribution and a diffusion element awaited both technical and theoretic developments This more definitive approach was based upon a knowledge of the nature of the partial pressures or gas tensions of carbon dioxide and oxygen in alveolar air and pulmonary capillary or mixed arterial blood (Table 2)

The concept of the relationship between ventilation and perfusion based upon measurements of the partial pressure of oxygen and carbon dioxide in the blood and gas phase in normal and abnormal states developed from the theoretic concepts dependent in part on the

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The partial pressure of a gas may be defined as that pressure exerted by it in a mixture of gases which it would exert if no other gases were present For example the partial pressure of carbon dioxide or oxygen in any medium can be simply calculated by multiplying the measured concentration of carbon dioxide or oxygen expressed as a percentage by the barometric pressure corrected for water vapor pressure

work of Krogh (50) Barcroft (9) and others (64) and so well synthesized by Riley and extended by Riley Cournand Rahn and others (34 38 69 75-77) It could then be shown that abnormalities of such ventilation–perfusion characteristics (Fig 2) could result in an abnormal gradient (pressure difference) between the alveolar partial

TABLE 2.—RESPIRATORY GASES AND GAS EXCHANGE ("NORMAL" RANGES IN AN ADULT MALE HOSPITAL POPULATION)

I	Respiratory gas content of whole arterial blood	
	CO content (vol %)	45-52
	O saturation (%) basal	94-98
	Following 30 step exercise	94-98
II	Pulmonary gas tensions (partial pressures in mm Hg at sea level)	
	Arterial P_{CO_2} (basal) (assumed equal to alveolar P_{CO_2})	35-40
	Alveolar P_{O_2} (calculated) (basal room air)	100
	Arterial Po (basal room air)	95-100
III	Alveolar arterial oxygen gradient (calculated mm Hg)	
	Room air level of inspired O	0-12
	Low O level	0-12
IV	Physiological Dead Space (calculated) (% of total ventilation)	30
V	O diffusing capacity (calculated)	> 15

pressure of oxygen and the arterial partial pressure of oxygen, with or without associated hypercapnia In the "normal" state in which each capillary is well perfused with blood in which each alveolus associated with that capillary is well ventilated and in which the total diffusing surface between this capillary and alveolus is normal, a small gradient exists between the partial pressure of oxygen in the alveolus and the partial pressure of oxygen in the arterial blood (Table 2) This gradient can be divided into two components (51) *(1)* The first is due to failure of the alveolar oxygen tension to reach equilibrium with the oxygen tension in the blood leaving the pulmonary capillary (membrane component) This gradient is in part the result of the relatively low solubility of oxygen *(2)* The second is caused by the addition of blood with lowered oxygen tension (mixed venous blood) to the blood distal to the pulmonary capillary This occurs in congenital heart disease with right to left shunt, in pulmonary arteriovenous fistula and in conditions with impaired ventilation of well perfused

areas in the lungs A true venous admixture is that found normally as a result of direct bronchial venous drainage into the pulmonary system †

Since carbon dioxide is far more soluble than oxygen it diffuses through the alveolar wall 15 to 25 times as swiftly as oxygen, and impairment of the membrane is rarely sufficient to cause a gradient for carbon dioxide between the alveoli and the arterial blood Thus any such gradient reflects disturbance in distributive factors and the arterial carbon dioxide tension is usually an index of the over all efficiency of alveolar ventilation When this is impaired the concentration of carbon dioxide in arterial blood rises ‡ The fact that under normal conditions arterial blood is in carbon dioxide equilibrium with alveolar air has been repeatedly confirmed (78) suggesting that normally there is no significant venoarterial shunt from bronchial veins and no uptake in the left ventricle The assumption of such an equilibrium is essential in the calculations derived from the methodology of Riley

These principles can be applied to the clinical study of gas exchange by a practical technic which permits the determination of the oxygen and carbon dioxide tensions in mixed arterial blood—the technic of Riley and Lilienthal (80) for direct measurement of these tensions by equilibration methods Once the arterial partial pressure of carbon dioxide is known the alveolar partial pressure of oxygen may be calculated from the alveolar formula (78) The difference between the alveolar and the arterial oxygen partial pressures represents the oxygen gradient Since either diffusion or distribution difficulties can cause an abnormal oxygen gradient recently developed technics must be used which permit the gradient to be determined at both room air and low oxygen levels of alveolar oxygen (51) The principles on

† EDITORS NOTE—Under normal conditions right auricular pressure and that in the azygos vein is lower than the pressure in the left auricle and pulmonary veins so that there is flow from the latter toward the former through anastomoses between bronchial and pulmonary veins With superior caval obstruction there may be considerable flow in the opposite direction leading to a significant alveolar arterial gradient due to venous admixture In mitral stenosis and in left heart failure the flow at these anastomoses is from left to right but in cor pulmonale the flow is reversed and this type of venous admixture contributes to the alveolar arterial gradient

‡ EDITORS NOTE—The heart muscle has a very high carbon dioxide tension and coronary venous blood is the least oxygenated in the body Although the blood passing through the left ventricle is separated only by the thin transparent endocardium from capillaries and muscle fibers rich in carbon dioxide there is no significant diffusion across this membrane

which these technics are based may be summarized as follows Normally any gradient at room levels of inspired oxygen is almost entirely a result of venous admixture a gradient occurring with low levels of inspired oxygen on the other hand mainly reflects disturbances of the

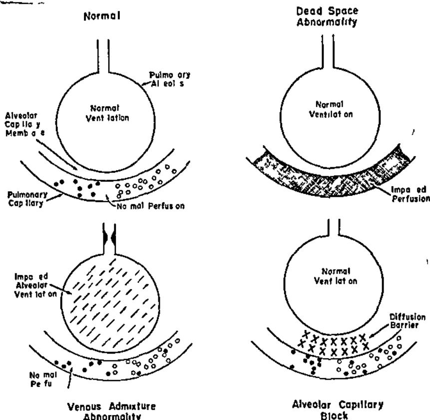


Fig 2 —Ventilation perfusion relationships

pulmonary membrane It is thus possible to separate any oxygen gradient into a diffusion and a distribution component

The dead space ventilation of the lung (Table 2) is that part of the total ventilation not contributing to gas exchange (76) It includes all of the tracheobronchial tree (anatomic dead space) and those areas of the lung that are ventilated but not perfused or poorly perfused (physiologic dead space) The importance of dead space can be seen by reference to Figure 2 It is quite apparent that as the dead space

enlarges effective alveolar ventilation is reduced resulting in a decrease in effective alveolar oxygen tension which in turn can lead to a decrease in arterial oxygen tension Normally the so called physiologic dead space approximates the anatomic dead space in which case ideal ventilation and perfusion relationships presumably obtain and the pulmonary membrane is normal In pulmonary emphysema and pulmonary fibrosis however the physiologic dead space may significantly exceed the anatomic dead space

Dead space is ordinarily calculated by the Bohr formula (24) once the arterial carbon dioxide tension is known The procedure is valid provided the measurement of arterial carbon dioxide tension is accurate Dead space may also be estimated by using oxygen nitrogen or helium Recent work suggests that results of these other methods check fairly well with those of the carbon dioxide method (10) Bateman (11) found that the dead space has a fairly constant value provided a steady state is maintained Others have shown that in the normal individual the dead space is independent of changing tidal volume (41) but whether this is necessarily true in a disease such as emphysema in which ventilation-perfusion relationships may vary is questionable In some 20 cases studied on two or more occasions in our laboratory the dead space values on room air levels of inspired oxygen checked fairly well in each study However when dead space is measured on low oxygen levels of inspired air the discrepancies are more serious (97) they may be related to hyperventilation and an unsteady state resulting from the anoxic stimulation of low oxygen levels Although recent methods for estimating dead space are more precise (41 43) they lack the routine clinical applicability of the Riley Cournand modification (24) of the Bohr method Oxygen diffusing capacity of the lung is defined as the oxygen uptake per minute per mean pressure gradient for oxygen between alveolus and capillary It is a useful index of the over all integrity of the area available for diffusion of gases and thus reflects the state of health of the pulmonary membrane The method as originally developed by Krogh (50) using carbon monoxide was primarily a research tool Riley and Cournand (75 77) developed an analytic method for deriving a diffusing capacity of the lung in a manner which permitted clinical applicability The measurement of diffusing capacity for oxygen (Table 2) at rest is a simple procedure requiring only the technical study of the gradients at two levels of oxygenation It seems probable that this measurement under conditions of stress might be of greater value since this would

eliminate borderline responses Routine study of this sort is somewhat difficult for the room air and low oxygen gradient must be determined under conditions which produce a steady state of exercise with maximal oxygen consumption The line charts available for these calculations also permit a rough estimation of the percentage of the cardiac output which is composed of venous admixture blood (75)

In general the oxygen diffusing capacity of the lung will be low when the oxygen consumption (on exercise) is low or when the membrane component of the alveolar arterial gradient is abnormally high A low oxygen consumption can result from inadequate pulmonary blood flow and occasionally from severe degrees of ventilatory insufficiency In one sense therefore the diffusing capacity of the lung summarizes the relative roles of perfusion ventilation and diffusion Riley *et al* (79) have measured diffusing capacity comparing the results obtained by the Riley Cournand method with those of a modified carbon monoxide method (40) In general there was good agreement between the results obtained by the two methods especially in the presence of gross gas diffusion abnormalities The Riley method therefore may be used for the study of most clinical problems

The validity of the gas exchange analyses just discussed largely rests upon the accuracy of the technic used to measure the blood and gas tensions Concern has been expressed regarding the method (39) The need for great precision of technic is obvious it is equally clear that even slight errors in mensuration may seriously affect the final results particularly that of the carbon dioxide tension It is for this reason that we routinely calculate the carbon dioxide tension from the pH and carbon dioxide content of arterial blood (89) which permits checking the direct measurement of the carbon dioxide tension In over 50 cases in which each patient was studied on two or more occasions under very similar circumstances excellent agreement was obtained between the measured and calculated carbon dioxide tensions (87)

In order to determine ventilation and gas exchange under stress it is usual to do some form of exercise study along with the resting studies The exercises are most often acute and no attempt is made to obtain a steady state The 30 step test of Baldwin Cournand and Richards (5) is such a test and may be used for clinical study as it provides gross means of detecting arterial oxygen unsaturation which is not present at rest In addition the ventilatory responses to such an exercise when carefully performed may be significant The exercise behavior of the alveolar arterial oxygen gradient cannot be analyzed

for the test does not permit achievement of a steady state Furthermore it does not allow the development of maximal responses so that borderline cases cannot always be separated from grossly normal or abnormal cases Lastly, because of brevity of exercise an untrained subject may react with ventilatory responses of an extreme nature which may be of little or no physiologic significance In a few cases such an exercise may give falsely positive results For example failure to reach a steady state may cause a mild degree of arterial oxygen unsaturation to develop which then may be interpreted as a clinical abnormality Usually when the same subject performs exercises for a longer period and achieves a steady state the oxygen saturation and ventilation are seen to be perfectly normal (87) The patient to be tested must be given some training and a great deal of encouragement in order to develop reasonable performance levels A more suitable type of exercise is that which utilizes the walking treadmill This provides maximal performances under steady state conditions and unlike bicycle exercises is rarely exhausting The treadmill also permits crude calculation of work so that comparative exercises can be more easily standardized in untrained subjects Occasionally good results may be obtained with a steady state passive exercise the stress of such an exercise can equal that of active exercise

A critical discussion of the problems arising from the use of these technics will be found in Volume 2 of *Methods in Medical Research* (24) With minor modifications they are now being generally used and most of the well documented clinical studies are based upon them Although their scope has grown larger and broader it may be fairly said that these methods are still the most valid for routine clinical purposes

PHYSICAL PULMONARY PROPERTIES AND RESPIRATION MECHANICS — The essential theory of the mechanical properties and behavior of the lung has long been known Rohrer (82) basing his work upon anatomic observations recognized that the pressure differences from the chest wall to the mouth determined the flow of gas throughout the tracheobronchial tree He clearly differentiated between the forces depending upon the state of pulmonary distention (elastic forces) and the forces resulting from friction within the entire pulmonary system The latter forces he considered to be a result of gas flow resistance within the tracheobronchial tree and of the resistance of the lung parenchyma itself (viscous forces) He related the forces of resistance to flow to a changing lung volume the elastic forces to a static lung

volume Rohrer also defined the physical principles of air flow in terms of turbulent and streamline flow He postulated that the difference in pressure between the chest wall and the mouth required to produce air flow was a simple function of the two types of resistance to air flow This could be defined by the general equation $P = K_1V + K V$ where P is the pressure gradient, V the rate of flow of respiratory gases K_1V the streamline flow and gas viscosity and K V the turbulent factor

According to some this general equation should include the forces of the internal friction of the lung (60) The static forces under constant lung volume could be similarly defined and it was shown that under conditions of zero air flow the intrathoracic pressure equaled the elastic forces of the lung The intrathoracic pressure under conditions of air flow is therefore equal to the algebraic sum of the elastic forces the forces required to overcome tissue resistance and those required to produce gas flow If the intrapleural pressure is measured under conditions of static lung volume and under conditions of gas flow the difference between the two measurements will represent the pressure change necessary to overcome resistance to gas flow along the tracheobronchial tree

Rohrer s simple theory has been confirmed and a number of technics have been developed to measure these forces Earlier methods measured the intrapleural pressure directly and the respiratory flow at the mouth by means of a pneumotachygraph (90) The investigators who expanded and amplified these methods found a great deal of evidence to substantiate Rohrer s original work (22 32 33 37 60 67 68) But the early workers encountered a number of difficulties *(1)* Intrapleural puncture entailed the risk of air embolism *(2)* It was difficult to separate static from kinetic forces *(3)* Analyses of the pressure volume and gas flow relationships proved to be an extremely tedious task with the apparatus then available With the demonstration that the intraesophageal pressure closely approximates intrathoracic and intrapleural pressures a better and simpler technic became available for these studies (15) The relative ease of recording the intraesophageal pressures at gas flow and zero gas flow periods has made it possible to apply the study of the elastic forces of the lung and the forces producing air flow to clinical problems (44 60 61) As ordinarily used these methods do not measure the forces and the work of the chest wall in respiration but the forces that operate between the pleural surfaces and the oral cavity Attempts have been made to measure the chest wall forces by passive ventilation in body respirators the pressure gradients ob

tained representing the difference between the respirator and mouth pressures (68) This pressure gradient can be related to the total forces causing air flow But since this measurement does not reflect the normal active ventilatory state its clinical usefulness is limited

The elastic forces of the lung may be thought of in the following manner The elastic recoil forces of the normally distended lung aided by passive forces of the chest wall will produce the normal expiration without any significant increase in work The balance between these forces determines the state of lung distention as the force of elastic recoil decreases so the lung will overdistend If the changes in intra esophageal pressure (under conditions of static lung volume) are plotted against the lung volumes a pressure volume curve defining these relationships can be drawn and the mean change in pressure per change in lung volume (100 cc increments) can be calculated It can then be shown that while this relationship is not absolutely linear the lung tension in normal individuals will vary directly with the lung volumes (32 44 61) For reasons that are not completely clear the actual measurements of this relationship have varied somewhat depending upon the investigator

It is well recognized from fluoroscopic and bronchographic evidence that the tracheobronchial tree expands and elongates during inspiration and contracts and shortens during expiration It is now clear that the elastic forces of the lung are primarily responsible for this behavior The noncartilaginous bronchioles have little intrinsic support as long as the intrathoracic pressure is less than the intrabronchial pressure (as in the normal elastic lung) these structures will remain patent In disease states in which pulmonary elasticity is diminished and the intrathoracic pressure rises these unsupported bronchioles tend to collapse particularly in expiration A disease such as emphysema will therefore show increased resistance to air flow during expiration (32 44)

McIlroy Marshall and Christie (60) have calculated the elastic and nonelastic forces in terms of respiratory work and estimate that in the normal subject about 70 per cent of the work expended in expiration is against the elastic forces of the lung They further suggest that in health and disease the rate and depth of breathing is controlled in a manner as yet unknown so as to minimize the work of respiration Preliminary study suggests that this may also hold true for an acute exercise state as well as the resting state

These nonelastic forces of the lung represent the pressure differences necessary to produce air flow along the tracheobronchial tree They can be calculated by means of the algebraic relationships noted above and they are analyzed and computed with similar technical set ups (44) Rohrer s concept of the relationship between pressure gradient and flow has been confirmed and it is agreed by most workers that turbulence and streamline flow are the major causes of resistance to air flow in normal subjects (16 44 61) These resistances increase significantly toward the end of expiration because of the tendency of unsupported bronchioles to collapse This may become very pronounced in the emphysematous patient The very slight resistance to inspiratory flow in the normal individual can become significant in disease states (67) On the basis of anatomic studies on emphysematous lungs it has been concluded that the internal friction of the lung is an important factor in producing air flow resistance (58) This point of view has been extended to physiologic observations with much the same conclusion (59) The majority of workers have not been able to confirm the importance of tissue resistance in causing air flow impedance (44 61)

The relationship between intrathoracic pressure gradient and flow rates is a curvilinear one which in the normal subject and in the emphysematous patient approaches an asymptote In the normal subject however this occurs at much higher levels and therefore to a certain degree respiratory flow can increase with increase in intrathoracic pressure gradient It can also be shown that increasing flow rates by means of rapid respiration can cause an increase at times marked in turbulence and therefore in air flow resistance (61) In such a case it is obvious that the work of respiration is tremendously increased and rapid respiration in almost any situation is therefore a very inefficient way of increasing air flow The phenomenon is even more apparent in emphysematous patients in whom such resistance to air flow together with the added resistance effect of bronchiole collapse due to loss of elasticity adequately explain the commonly observed obstructive spirogram These observations also suggest that spirography and the test of maximal breathing capacity should be done under conditions which encourage the patient to breathe rapidly in order to detect borderline cases of bronchial obstruction Fluoroscopy will demonstrate the effect of rapid respiration on the bronchioles in emphysema by showing that with rapid and forceful respiration the diaphragm tends

to assume the full inspiratory position, indicating increasing resistance to air flow concurrently, the walls of major bronchi and the trachea tend to approximate each other especially toward the end of a rapid expiration

CLINICAL STUDIES IN PULMONARY PHYSIOLOGY

Pulmonary Emphysema

Intensive study of pulmonary emphysema has resulted in extensive knowledge of its pathophysiology Some understanding of this is essential for a rational approach to therapy

The lung volumes in generalized pulmonary emphysema ordinarily reveal some reduction in vital capacity and some increase both in the absolute value for residual air and in the ratio of residual air to total lung volume (greater than 30 per cent) (6) An increase in the ratio of residual air to total capacity does not in itself necessarily indicate emphysema significant reductions in vital capacity due to fibrosis of the lung or pulmonary congestion in the presence of a normal residual air will also cause an increase in this ratio Hyperinflation of the lung from other causes will also elevate the residual air to a certain degree (25) In advanced emphysema however this ratio is very significantly increased and it is not uncommon to find the residual air accounting for 70 per cent of the total lung volume The vital capacity is apt to be more variable and may be normal in mild cases but with time will become reduced because of the overdistended state of the lung

The mechanical difficulties resulting from the deformity of the chest wall the muscular incoordination the loss of pulmonary elasticity and the presence of bronchial obstruction have been repeatedly observed (6 22 49) These abnormalities are best reflected in a qualitative sense in the spirograms and the maximal breathing capacity Characteristically the spirogram reveals delay in emptying the lung as well as reduction in volume of gas expelled In advanced cases the lung tends to remain in an inspiratory position so that the spirogram returns *very slowly or not at all to the base line* indicating air trapping due to bronchial obstruction All of the factors which maintain maximal breathing capacity are abnormal in pulmonary emphysema Particularly important are the presence of bronchial obstruction and the loss of pulmonary and possibly chest wall elasticity which cause a significant reduction of maximum breathing capacity to as little as 15 liters per minute

The physical properties of the lung and their effects upon the mechanics of ventilation as they relate to pulmonary emphysema can be considered as follows As a result of loss of pulmonary elasticity together with the bronchial obstruction due to the bronchitis which is present in emphysema the pressure gradient required to produce gas flow in both expiration and inspiration is increased (44, 59) but a point is very quickly reached at which, despite significant increase in pressure gradient, there is no further increase in gas flow The increase *in respiratory rate which occurs as a compensatory mechanism* also adds to the expiratory obstruction further placing the emphysematous patient in a mechanically unsound situation (61) The expiratory obstruction is mainly a result of increased resistance to turbulent and laminar flow in the bronchial tree (44 61) In addition, the effect of the inelastic lung upon the bronchiolar diameter will tend to cause some collapse of bronchioles further increasing resistance to gas flow This is particularly true when the intrathoracic pressure rises greatly as a result of active expiratory effort (32, 44) It has not yet been established whether the viscous resistance of the lung parenchyma is such as to add to the resistance to air flow (44 59) As a result of these abnormalities the patient with emphysema in contrast to the normal individual produces his expiration in an active manner This work must be met by increased oxygen consumption (16)

McIlroy and Christie (59) have suggested that the greatly increased work of ventilation in the emphysematous subject is due chiefly to the increase in the nonelastic resistance of the lung tissue In turn they relate the latter factor more to increased viscosity of the lung than to bronchial obstruction Experiments by this group of workers utilizing hydrogen breathing (rather than ordinary room air) have demonstrated that the resistance to air flow in normal subjects can decrease by half and similarly there is a considerable reduction in air flow resistance in patients with bronchospasm In emphysematous patients on the other hand hydrogen breathing causes a comparatively small decrease in resistance to air flow This implies that whereas in the normal subject most of the work of respiration is accomplished by overcoming elastic *resistance to stretch during inspiration (rebound of the* stretched fibers therefore supply energy for expiration) in the emphysematous patient most of the respiratory work is accomplished during expiration at which time bronchial resistance is at its maximum and the viscous inelastic lung returns little of the energy used in its expansion

Careful clinical observation has convinced most workers that the dyspnea in pulmonary emphysema can be related to the work needed to maintain ventilation and the mechanical difficulties which tend to prevent or limit this increase in work (6 49 59) The emphysematous patient is constantly "working" even at the slightest activity Obviously this work demand could well make the patient conscious of his respiratory efforts The relation between work demand and ability to produce work is also implied in the concept of breathing reserve (5), which may be defined as the difference between the maximal breathing capacity and the actual ventilation requirements of any performance (73) This figure may be expressed as a percentage of the maximal breathing capacity Cournand *et al* (29) have correlated the appearance of the subjective sensation of dyspnea in normal subjects and in emphysematous patients with the lowering of the breathing reserve to 60 or 70 per cent of the maximal breathing capacity Recent attempts to re assess the work of breathing in terms of oxygen consumption may throw additional light upon the mechanisms of dyspnea

The distribution of inspired gases in emphysema is also variably disturbed depending upon the degree and nature of the mechanical difficulty The percentage of alveolar nitrogen measured by Darling's method reveals abnormalities in a significant number of cases The method however is not very sensitive and is readily influenced by uneven alveolar ventilation and hyperventilation (5, 26)

The oxygen consumption at rest and on exercise may be within normal limits in moderate emphysema In advanced stages of the disease the exercise oxygen consumption may be low as a result of inadequate ventilatory responses Concomitant cor pulmonale and cardiac failure may also lower the exercise oxygen consumption Furthermore the loss of lung surface available for gas exchange may be such as to reduce oxygen consumption even more especially under conditions of stress (74)

Dead space may be within normal limits in emphysema In time it will increase further reducing effective alveolar ventilation The physiologic abnormalities described above characterize emphysema as a disease in which both ventilatory function and gas distribution are profoundly impaired Many patients with emphysematous ventilatory insufficiency will maintain fairly normal arterial oxygen saturation and carbon dioxide content so long as effective hyperventilation is maintained and exercise stress is at a minimum With sufficient exercise

however mild arterial oxygen unsaturation usually develops which may progress until it is present at rest With further impairment of ventilation–perfusion relations, profound anoxia of the arterial blood may occur accompanied by varying degrees of hypercapnia and respiratory acidosis In many of these patients cardiac failure due to cor pulmonale will then develop

Detailed studies of gas exchange and alveolorespiratory function will usually reveal an increased alveolar arterial oxygen gradient when the patient is tested in room air or at high oxygen level In our experience this is true even when there is sufficient ventilatory function to prevent the appearance of arterial oxygen unsaturation at rest The increase in distribution gradient is due to abnormal ventilation–perfusion relations and when sufficiently great will produce arterial oxygen unsaturation and hypercapnia Absence of gross arterial oxygen unsaturation in patients with ventilatory insufficiency and abnormal distribution gradients can be explained on the basis of the relation obtaining between the partial pressure of oxygen and the oxygen saturation in arterial blood (oxygen dissociation curve) At high levels of arterial oxygen saturation rather large changes in the partial pressure of oxygen cause only small changes in arterial oxygen saturation The arterial partial pressure of oxygen may therefore be 10 to 15 mm Hg lower than normal while the arterial oxygen saturation remains within the lower limits of normal This is why the detection of gas exchange difficulties requires measurement of the partial pressures of oxygen in the blood and gas phase of respiration

In some patients with advanced emphysema the venous admixture due to inadequate alveolar ventilation may be extremely large Precise measurements of the magnitude of this physiologic shunt are not available but rough calculation in some of our patients suggest that 25 to 50 per cent or even more of the total pulmonary blood flow is actually being shunted In several patients in preterminal stages arterial oxygen saturation as low as 30 per cent have been found These patients have distribution gradients in the order of 50 to 60 mm Hg, and obviously are extreme examples In addition such patients are usually in cardiac failure a factor which may well effect the gradient

In a small number of patients definitely abnormal results have been observed in low oxygen studies (87) They also manifest a low oxygen diffusing capacity especially with exercise Riley (74) has evidence that the maximal diffusing capacity under conditions of prolonged steady state exercise may be abnormally low in some cases The ex

planation for this abnormality and its clinical significance is not altogether clear It may be related to loss of functional tissue due to the disease process cardiac failure due to cor pulmonale and the presence of polycythemia could also contribute to the low figures

Significant retention of carbon dioxide in the arterial blood is a logical development of the inadequate ventilatory mechanism in emphysema Early, it may be only minimal and without much clinical significance and there is usually sufficient hyperventilation to prevent further hypercapnia If however the over all ventilatory capacity is extremely low (severely reduced maximal breathing capacity) or if hyperventilation of functioning alveoli is further impaired by concomitant bronchial infection or if the respiratory center becomes depressed hypercapnia and respiratory acidosis become clinically significant (85) Severe reduction of maximal breathing capacity is rarely an important factor in respiratory acidosis There is little question that in most cases the initiating factor is ineffective alveolar ventilation, usually aggravated by acute bronchial obstruction due to infection Sustained hypercapnia may then develop over a period of some hours At this stage depression of the respiratory center usually becomes evident and is most obviously reflected in hypoventilation which in turn perpetuates the hypercapnia This basic phenomenon—the lack of respiratory center drive in response to carbon dioxide retention—progresses until the only remaining respiratory stimulus is that due to the stimulus of anoxia on the carotid centers (27) Oxygen therapy may further eliminate or suppress this respiratory drive unless the patient is promptly treated carbon dioxide narcosis will occur with resultant coma and death (85)

Rahn and Otis (70) studying unacclimatized persons at high altitudes have found that an increase in the blood bicarbonate level will depress the respiratory center response to carbon dioxide thereby compensating for the high altitude alkalosis In the emphysematous patient with hypercapnia and normal renal function the blood carbonic acid by direct stimulation of the renal tubules causes reabsorption of increasing amounts of bicarbonate and the pH of the blood tends to return to more normal levels so that in effect the respiratory acidosis becomes compensated (71) This increase in blood bicarbonate level may depress the respiratory stimulus somewhat which in turn perpetuates ventilatory depression and hypercapnia

A recent study of carbonic anhydrase inhibitors in emphysematous patients with carbon dioxide retention also seems to implicate excess

bicarbonate as a respiratory center depressant (65) In such patients carbonic anhydrase inhibitors may produce a decrease in blood carbonic acid content, if the hypercapnia is of mild degree The drop in blood carbon dioxide is preceded by that of blood bicarbonate level, which in turn is due to the renal loss of bicarbonate This is additional evidence that the bicarbonate in the blood can directly depress the respiratory center and that the temporary removal of base by carbonic anhydrase inhibitors may permit more effective ventilation (88) In more advanced cases of pulmonary emphysema with hypercapnia lowering of the blood bicarbonate level does not cause a significant decrease in carbon dioxide tension indicating a less than normal increase in ventilatory drive (46) These patients moreover do not manifest an increase in ventilation when carbon dioxide is added to the inspired air either before or after the blood bicarbonate level is artificially reduced by means of carbonic anhydrase inhibitors (42) The conclusion that permanent damage of the respiratory center is present in such cases seems reasonable It would explain the dependence of the patient with advanced emphysema and hypercapnia upon the sensitivity of the carotid body to arterial anoxia

In chronic pulmonary emphysema with superimposed acute respiratory acidosis we have been unable to demonstrate any significant drop in blood carbon dioxide tension as a result of decrease in the bicarbonate content of the blood (87) The only effect noted was the development of decompensation of the respiratory acidosis with the production of a rather low pH The effect of acidifying salts such as ammonium chloride resembled that of carbonic anhydrase inhibitors decreasing blood bicarbonate levels without a significant drop in the blood carbonic acid Riley (74) has recently suggested that respiratory acidosis in pulmonary emphysema might be considered a compensatory mechanism which makes the work limitations of such patients tolerable (74) These patients with severe respiratory acidosis are usually in cardiac failure due to cor pulmonale and this in turn can be related to the pulmonary hypertension which is so much a part of the picture in advanced emphysema The clinical features of this stage described by Stone and associates (85) have been confirmed by an increasing body of experience The pulmonary hypertension is the result of many factors such as reduced vascular bed increased blood volume polycythemia, hypercapnia (30) and arterial oxygen unsaturation

Prolonged anoxia will cause secondary polycythemia in some pa

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demonstrated by improvement in the spirogram though not all to the same degree In the presence of cardiac failure digitalization is indicated and is effective (30) Phlebotomy is also helpful if secondary polycythemia is present the benefit may be due to the removal of the depressant effect of the polycythemia upon the respiratory center (70) and possibly to the effect on the mechanics of ventilation by the reduction in red cell mass To decrease the work of breathing the wasteful and ineffective energy expenditure of the accessory muscles of respiration should be abolished and an attempt made to correct the dysrhythmic breathing which is so much a part of the clinical picture This can best be accomplished by the use of respiratory exercises in conjunction with bronchodilators Exercises which strengthen abdominal muscles and stress passive expiration with as little active expiration as possible are to be preferred Good examples of this type of retraining are some recently reported respiratory exercises (62)

Pneumoperitoneum which occasionally will decrease the functional residual air has been advocated for the treatment of chronic pulmonary emphysema (19) Thorough study of 5 patients before and after prolonged use of pneumoperitoneum revealed no significant change for better or worse in any factor although initially some patients experienced subjective improvement (87) Pneumoperitoneum like any factor that can increase intra abdominal pressure may have an unfavorable effect upon the mechanics of respiration Raised intra abdominal pressure can increase intrapleural pressure and this may have an adverse effect on the work of breathing The final evaluation of pneumoperitoneum will require study of the pulmonary physical properties under such conditions Dramatic benefit from pneumoperitoneum occurs in an occasional case of respiratory acidosis (17) we have had one such experience It is apparent that limitation of physical activity will reduce the work demands of the emphysematous patient rest, particularly during periods of acute respiratory infection or cardiac failure is therefore indicated

The treatment of the severer states of emphysema with respiratory acidosis has been described and discussed in detail elsewhere (85) Increasing experience with such patients has convinced our group that the mechanical respirator with cyclic negative and positive pressure changes is the most efficient means of ventilating these patients artificially and there is good evidence that adverse circulatory effects under such conditions are minimal (54) Continuous oxygen therapy should

tients usually most marked when cardiac failure and/or respiratory acidosis develop In our experience about 50 per cent of such patients will show polycythemia The reason why more patients do not manifest it may be related to the extremely poor nutritional state of many of the patients The importance of secondary polycythemia in respiratory acidosis lies in its possible effect upon the respiratory center The red cell is an important carrier of base because of its carbon dioxide buffering action and it has been suggested that polycythemia itself will add to the depressant effect of bicarbonate on the respiratory center (70), the magnitude of this effect has not been measured In addition *circulatory stasis accompanies polycythemia and intravascular thrombosis may occasionally result* This too could possibly affect the response of the respiratory center in patients with polycythemia pathologic evidence however is scanty

We have encountered 4 examples of an interesting clinical variant of this type of respiratory acidosis Severe shock with oliguria and anuria, developed in all 4 patients during the phase of acute respiratory acidosis In 3 of them the shock lasted several days and despite temporary improvement in the respiratory acidosis and maintenance of blood pressure for a short time with norepinephrine all 3 died Post mortem examination did not reveal the cause of this shocklike state The fourth patient recovered with the same treatment Possibly, these patients suffered severe damage of their vasomotor centers as a result *of the acidosis and anoxia with consequent loss of normal cerebral* vasomotor tone (87) followed by shock and acute renal shut down

In all the fatal cases of respiratory acidosis in our series the arterial pH terminally was 7 2 or lower with carbonic acid levels of 90 mm Hg or above This in itself is of no prognostic value as an occasional patient with such derangements recovers with proper treatment

It seems obvious from the nature of the physiologic abnormalities in pulmonary emphysema that basically therapy must be oriented toward decreasing the work of breathing and increasing the effective alveolar ventilation This can best be accomplished through decreasing bronchial resistance to air flow by the use of bronchodilating agents antibiotics and steam inhalation for the control of inflammatory obstruction and occasional careful use of ACTH or cortisone to suppress inflammatory bronchial responses of a possible allergic nature Bronchodilators should be used even in the absence of audible wheezing for most patients will respond to such therapy as can be

BULLOUS EMPHYSEMA

Functionally this disease can be considered as a localized form of pulmonary emphysema in which air trapping leads to cyst formation. It is an acquired rather than a congenital disease occurs in all age groups and is a process in which localized bronchial obstruction appears to be the initiating factor (3) As with generalized emphysema it may appear without apparent cause it may occur with an organizing fibrosis or commonly as a complicating factor in generalized pulmonary emphysema

The functional picture of bullous emphysema depends upon *(1)* size and volume of the bullae *(2)* patency of the communication between bullae and tracheobronchial tree and *(3)* presence or absence of generalized pulmonary emphysema To these groups may be added a fourth category that of generalized bullous emphysema in which the bullae are much smaller and the over all effect is physiologically identical to generalized pulmonary emphysema

Baldwin *et al* (8) have described the physiologic abnormalities which depend upon these factors in general bullous emphysema can have several grossly recognizable functional patterns Most commonly large isolated air cysts are found with normal or slightly elevated residual air and lung volumes in such cases the over all ventilatory mechanism is well preserved because the isolated "cysts" usually do not trap significant amounts of air in expiration The mechanics of ventilation as reflected in the spirogram and maximal breathing capacity are fairly normal

Gas exchange studies may occasionally reveal some increase in dead space if the cyst is large enough the increase may be enough to reduce effective alveolar ventilation and produce mild degrees of arterial blood anoxia This was almost invariably true in some 16 cases studied by the author In addition differential bronchospirometry in these cases revealed some degree of reduced oxygen consumption on the side of the lesion Any procedure designed to eliminate these large isolated bullae is followed by a demonstrable return to normal of the differential oxygen consumption figures (87) Of greater significance functionally are cases of isolated bullae with communications which are intermittent or of such a nature that air trapping can be detected by fluoroscopy or spirography As a result of air trapping the bullae especially during expiration compress the remaining normal lung

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In the usual case of pulmonary emphysema there is both clinical and functional evidence to suggest that bronchitis with bronchial obstruction is the earliest "lesion" preceding by some time the loss of pulmonary elasticity While the latter may possibly be a result of bronchial obstruction it cannot be denied that parenchymal infection may contribute to the loss of elastic structure The thesis that bronchial obstruction is the most common anatomic lesion associated with emphysema is supported by some evidence (84) but cases are known in which the emphysema is accompanied by a minimal degree of organic bronchial obstruction Examples of this are *(1)* the overdistention or hyperinflation of a lung or lobe following resection *(2)* the emphysema and bullous emphysema which develops in areas of rapidly organizing fibrosis and *(3)* cases of chronic pulmonary emphysema with all the functional abnormalities of an inelastic lung but with very little history or physiologic evidence of a primary bronchial obstruction due to infection The small group of patients in the last mentioned category tends to manifest hyperventilation even at rest more readily than the usual case of emphysema and will have a low or normal blood content of carbon dioxide due to the hyperventilation In our experience oxygen therapy in these patients does not entail the risk of respiratory acidosis The functional derangement is superficially similar to that of certain types of fibrosis It would seem that in this type of pulmonary emphysema the patient may have a very low maximal oxygen diffusing capacity and that this may be the primary basis for the anoxia rather than the usual cause Although the anatomic evidence for a primary loss of elastic tissue is scanty it seems likely that this may occasionally occur and would explain some of the differences observed in the clinical pictures In time of course the loss of elasticity may promote bronchial infection and bronchial obstruction and the end stages then merge and perhaps no longer be completely distinguishable It has also been noted that such severely anoxic emphysematous patients with hyperventilation respond rather poorly to bronchodilating drugs (87) It must be emphasized however that this variant of pulmonary emphysema is uncommon clinically

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Functionally this disease can be considered as a localized form of pulmonary emphysema in which air trapping leads to cyst formation It is an acquired rather than a congenital disease occurs in all age groups and is a process in which localized bronchial obstruction appears to be the initiating factor (3) As with generalized emphysema it may appear without apparent cause it may occur with an organizing fibrosis or commonly as a complicating factor in generalized pulmonary emphysema

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Baldwin *et al* (8) have described the physiologic abnormalities which depend upon these factors in general bullous emphysema can have several grossly recognizable functional patterns Most commonly large isolated air cysts are found with normal or slightly elevated residual air and lung volumes in such cases the over all ventilatory mechanism is well preserved because the isolated "cysts" usually do not trap significant amounts of air in expiration The mechanics of ventilation as reflected in the spirogram and maximal breathing capacity are fairly normal

Gas exchange studies may occasionally reveal some increase in dead space if the cyst is large enough the increase may be enough to reduce effective alveolar ventilation and produce mild degrees of arterial blood anoxia This was almost invariably true in some 16 cases studied by the author In addition differential bronchospirometry in these cases revealed some degree of reduced oxygen consumption on the side of the lesion Any procedure designed to eliminate these large isolated bullae is followed by a demonstrable return to normal of the differential oxygen consumption figures (87) Of greater significance functionally are cases of isolated bullae with communications which are intermittent or of such a nature that air trapping can be detected by fluoroscopy or spirography As a result of air trapping the bullae, especially during expiration compress the remaining normal lung

not be used for the dyspnea of chronic pulmonary emphysema for fear of producing acute respiratory acidosis Intermittent oxygen therapy or oxygen together with artificial respiration can be safely used in acute situations Sedation and narcotics must be used with extreme care if at all in order to avoid further depression of the respiratory center

In the usual case of pulmonary emphysema there is both clinical and functional evidence to suggest that bronchitis with bronchial obstruction is the earliest "lesion" preceding by some time the loss of pulmonary elasticity While the latter may possibly be a result of bronchial obstruction it cannot be denied that parenchymal infection may contribute to the loss of elastic structure The thesis that bronchial obstruction is the most common anatomic lesion associated with emphysema is supported by some evidence (84) but cases are known in which the emphysema is accompanied by a minimal degree of organic bronchial obstruction Examples of this are (1) the overdistention or hyperinflation of a lung or lobe following resection (2) the emphysema and bullous emphysema which develops in areas of rapidly organizing fibrosis and (3) cases of chronic pulmonary emphysema with all the functional abnormalities of an inelastic lung but with very little history or physiologic evidence of a primary bronchial obstruction due to infection The small group of patients in the last mentioned category tends to manifest hyperventilation even at rest more readily than the usual case of emphysema and will have a low or normal blood content of carbon dioxide due to the hyperventilation In our experience, oxygen therapy in these patients does not entail the risk of respiratory acidosis The functional derangement is superficially similar to that of certain types of fibrosis It would seem that in this type of pulmonary emphysema the patient may have a very low maximal oxygen diffusing capacity and that this may be the primary basis for the anoxia rather than the usual cause Although the anatomic evidence for a primary loss of elastic tissue is scanty, it seems likely that this may occasionally occur and would explain some of the differences observed in the clinical pictures In time of course the loss of elasticity may promote bronchial infection and bronchial obstruction and the end stages then merge and perhaps no longer be completely distinguishable It has also been noted that such severely anoxic emphysematous patients with hyperventilation respond rather poorly to bronchodilating drugs (87) It must be emphasized however that this variant of pulmonary emphysema is uncommon clinically

RESTRICTIVE VENTILATORY INSUFFICIENCY

The obstructive features so characteristic of emphysema are absent in this type of ventilatory insufficiency and for that reason is rarely as of profound degree as in emphysema Restrictive ventilatory difficulty can be divided into *(1)* that due to varying degrees of pulmonary fibrosis *(2)* that due to restriction of the chest cage from any cause and *(3)* that due to impaired ventilatory drive either as a result of primary disturbances of the respiratory center or respiratory center abnormalities secondary to other diseases such as bulbar poliomyelitis

It can be argued that abnormalities of the respiratory center are not truly speaking examples of restrictive difficulties but we have found this classification desirable for didactic purposes Furthermore while bronchial obstructive features are not characteristic of this group they may develop in time due to organizing fibrosis and bronchial infection Last it must be recognized that etiologic factors cannot be neatly pigeonholed into separate functional types for there are diseases such as sarcoidosis in which several of the functional patterns can be manifested (86)

There are many diseases which produce pulmonary fibrosis They can be divided into two major groups *(1)* a larger group with varying degrees of ventilatory difficulty but without significant gas exchange difficulties and *(2)* a somewhat smaller group with pronounced difficulty of gas exchange mainly from interference with gas diffusion Pulmonary fibrosis which produces mild to moderate ventilatory insufficiency is as a rule clinically and functionally benign except when complicated by pulmonary emphysema Among the diseases in this group are some pneumoconioses such as uncomplicated silicosis some forms of Boeck s sarcoid fibrosis following diffuse pulmonary tuberculosis or miliary tuberculosis radiation fibrosis and a miscellaneous group of uncertain etiology (repeated pulmonary infection may be a factor) (7)

In general there is only a slight reduction of vital capacity a somewhat lowered or even occasionally normal residual air and slight to moderate reductions of maximum breathing capacity with values of less than 70 per cent of normal quite uncommon The spirogram ordinarily does not reveal airtrapping or obstruction The ventilation measurements in this group usually reveal significant degrees of hyperventilation especially during the first few minutes of recovery from

tissue and may even shift the mediastinum Varying degrees of ventilatory insufficiency result and disturbances of gas exchange can occur characterized by the presence of significant venous admixture This does not necessarily indicate that the uninvolved lung is diseased Such bullae tend to compress uninvolved parenchyma and on angiocardiographic study major pulmonary arterial vessels are usually found to be seriously compressed Ventilation and oxygen consumption on the affected side can therefore be considerably reduced (87) This is an example of some of the mechanical difficulties in bullous emphysema It is in such cases that surgical removal has had the best results It had at one time been suggested that with isolated bullae of this type arterial oxygen saturation may be normal (8) but further experience has shown that gas exchange may be impaired Presumably flow through the blood vessels despite their severe compression is sufficient to cause some imbalance in ventilation-perfusion relationships

The third functional pattern observed in bullous emphysema occurs in a rather large group and combines the functional difficulties due to large air trapping bullae with those of generalized emphysema Varying degrees of ventilatory insufficiency may therefore be combined with serious gas exchange difficulties with occurrence of respiratory acidosis and cardiac failure

The treatment of bullous emphysema is on the whole that described by Baldwin *et al* (8) Generally when an isolated bulla is discovered on a roentgenogram and the patient manifests no signs of ventilatory dysfunction surgical resection is not indicated Function studies are performed at yearly intervals and if ventilatory difficulty can be demonstrated surgery is then advised In many cases significant and lasting restoration of function has followed such treatment It was at first felt that treatment of localized bullae in the presence of severe pulmonary insufficiency was inadvisable but experience with several such cases has engendered a more optimistic view Localized bullae complicating generalized emphysema are not excised surgically but are rather obliterated by combining local chemical irritation with substances such as silver nitrate and direct catheter drainage Successful obliteration of large air trapping cysts was accomplished in 4 cases and the eventual re expansion of compressed lung tissue although quite emphysematous resulted in improved ventilatory function and increased work tolerance In advanced cases these methods are preferable to surgical excision

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exercise Occasionally the hyperventilation is so extreme that the breathing reserve is severely encroached upon and dyspnea during exercise and recovery may be the outstanding complaint (86)

Gas exchange studies may reveal mild degrees of arterial oxygen unsaturation with exercise but serious gradient abnormalities and anoxia are uncommon Hypercapnia is also extremely rare in fact, hypocapnia due to hyperventilation is not uncommon Values for oxygen consumption with rest and exercise dead space and index of intrapulmonary mixing tend to be normal

It is interesting that the usual stimuli for the hyperventilation such as anoxia hypercapnia and acidosis are lacking and the condition has therefore been attributed to reflex stimulation arising in the lungs (7) In most cases the ventilatory insufficiency and the subjective sensation of dyspnea can be related to the hyperventilation and the moderate reduction in ventilatory capacity

In our experience a patient with this type of ventilatory difficulty tends to remain functionally and clinically stationary for many years and deterioration is uncommon In no case has 5 year follow up on a fair number of patients of this type revealed the development of alveolorespiratory insufficiency and cor pulmonale (87) It has also been noted that when severe malfunction develops in benign fibrosis in diseases such as sarcoid it is apt to occur quite early in the disease and is characterized either by emphysema like patterns or by those abnormalities which interfere with gas diffusion (86) In general roentgenographic features of fibrosis cannot be correlated with disturbances of function (7) the nature and location of the lesions being of greater importance in determining the physiologic state Despite attempts to study and correlate the findings in various pulmonary diseases complete pathologic data to explain abnormal function are lacking Studies on sarcoid and miliary tuberculosis illustrate the difficulty of correlating the clinical and pathologic picture with the functional picture (56 57 86) For example cases of pulmonary nodal sarcoid without roentgenographic evidence of parenchymal disease have shown functional patterns of mild to moderate ventilatory difficulty similar to cases with marked roentgenographic changes (86) There is a general tendency to equate the degree of fibrosis with the reduction in residual air and total lung volume While this correlation may obtain in some cases occasionally a disproportion between the severity of lung volume shrinkage and the over all ventilatory function

is found Moderately reduced lung volumes in themselves therefore do not necessarily indicate malfunction

There is a miscellaneous group of processes in which the effective bellows action of the chest is impaired due to disease of the respiratory muscles disease of the integument of the chest wall diseases of the bony framework and possibly extensive pleural disease The degree of ventilatory insufficiency may be very mild and the patterns revealed by lung function studies may resemble those of benign fibrosis with one important difference in function this group usually does not show significant hyperventilation unless anoxia or hypercapnia is present Examples of mild impairment of ventilatory capacity include diseases of the bony framework such as kyphoscoliosis Marie Strumpell spondylitis neuromuscular disease due to neurologic or muscular dystrophies and rarer diseases such as scleroderma of the chest wall (20) Miscellaneous conditions which can produce varied degrees of ventilatory difficulty include phrenic nerve or diaphragmatic injury pleurisy pneumothorax thoracoplasty defects and possibly pleural calcification (36)

The functional picture is characterized by relatively normal to greatly reduced vital capacity residual air and total lung volumes mild to moderately severe reductions in maximal breathing capacity and breathing reserve ordinarily without an obstructive spirogram usually normal indices of alveolar ventilation and fairly normal dead spaces

Oxygen consumption with exercise may be normal, but if ventilatory capacity is severely restricted it may be quite low as in a moderate bilateral pneumothorax

Gas exchange and alveolorespiratory function is normal in the cases with mild or moderate restriction of ventilation and such cases are indistinguishable functionally from the benign fibrosis group In the severe cases such as the progressive neuromuscular diseases of the chest wall marked alveolorespiratory insufficiency occurs due to chronic hypoventilation This particular functional disorder is characterized by poor effective alveolar ventilation with subnormal alveolar and arterial oxygen tensions and the presence of significant venous admixture due to inadequate alveolar ventilation Hypercapnia and respiratory acidosis may therefore occur (36) Finally as a result of the anoxia secondary polycythemia and hypervolemia may develop followed by pulmonary hypertension and cor pulmonale

Despite the many stimuli for hyperventilation in this advanced type of restrictive ventilatory insufficiency, it rarely occurs Clinically significant hypoventilation is occasionally present either due to very severe restriction of chest bellows action or to secondary respiratory center involvement *Physiologically* the patient at this stage resembles in many respects one with advanced pulmonary emphysema in the presence of respiratory infection or with injudicious use of oxygen therapy, acute respiratory acidosis may develop The residual air determination and the spirogram together with the clinical picture should serve to distinguish the cases of emphysema and obstructive ventilatory insufficiency from this group of severe restrictive ventilatory insufficiency

Sometimes however the development of emphysema renders the clinical and the functional picture even more complex The ineffective movement of the chest cage may promote bronchial infection and bronchial fibrosis with resultant emphysema

An extremely interesting example of the development of cor pulmonale due to severe ventilatory restriction has been recently observed and reported (36) The patient had amyotrophic lateral sclerosis with marked involvement of the chest wall and diaphragmatic muscle resulting in a rapidly progressive ventilatory insufficiency characterized by a very low and unsustained maximal breathing capacity normal residual air and a nonobstructive spirogram Subsequently, anoxia hypercapnia and secondary polycythemia developed Death was due to cor pulmonale Postmortem examination did not reveal any significant intrinsic pulmonary disease to account for the physiologic abnormalities This case is significant for it demonstrates that combined ventilatory and alveolorespiratory insufficiency may occur even in the absence of basic pulmonary disease

Ventilatory Insufficiency Due to Respiratory Center Disturbances

Ventilatory drive may be reduced as a result of *(1)* disturbances of the respiratory center secondary to extrinsic diseases and processes such as drug poisoning emphysema and idiopathic polycythemia and (2) primary damage of the respiratory center due to neurologic disease such as tumor poliomyelitis or brain injury

The secondary disturbances in ventilatory drive were discussed earlier It was pointed out that evidence suggested the presence of

both a reversible and an irreversible depression of the respiratory center The reversible element was defined in terms of the effect of increased blood bicarbonate content upon the center and the irreversible element in terms of permanent damage to the center presumably a result of long standing hypercapnia Metabolically induced hypoventilation has also been observed in alkalosis with improvement of ventilation following relief of the alkalosis (1)

The depression of ventilatory drive resulting from poisoning of the medullary centers by drugs such as morphine or barbiturates is well recognized and needs no further discussion It is noteworthy that recently analogues of morphine have been advocated for treatment of morphine depression of respiration (35) In general severe respiratory depression due to drugs requires artificial respiration best given by the cyclic mechanical respirator

The relation between polycythemia and respiratory drive is complex The possible depressant effect of secondary polycythemia upon the respiratory center has been attributed to the increase in alkali due to the buffering action of the red cell upon carbon dioxide (70) Whether this is the only effect of polycythemia upon the respiratory center is not completely established and the possibility of actual damage to the center independent of the above mechanism must be considered The physiologic evidence for direct medullary center depression due to polycythemia rests upon recent observation of cases of idiopathic polycythemia (66) These patients were a clinically heterogeneous group but revealed no evidence of emphysema other pulmonary disease congenital heart disease or neuromuscular disease The common denominator of the group was polycythemia of varying degree presumably idiopathic

Follow up over a 3 year period has not revealed the development of any mechanism to account for a secondary polycythemia Our interest in this group lies in the fact that some of the studies suggested a primary effect of the polycythemia upon respiratory function independent of the depressant effect of increased blood alkali In 1 patient particularly there was a striking disproportion between ventilatory ability as reflected by a very good maximal breathing capacity and actual ventilation under conditions of stress At such times hypoventilation with exercise was so severe that arterial oxygen unsaturation became marked In addition both his blood bicarbonate level and pH were within normal limits so it must be concluded that there was a direct effect of the polycythemia itself upon the respiratory center

Furthermore phlebotomy completely restored his ventilatory responses to normal Serial studies in this patient have shown that abnormal ventilatory responses returned with each recurrence of the polycythemia A similar ventilatory response has been observed in another patient with essential polycythemia although phlebotomy did not correct the pattern of hypoventilation Presumably this case represents a more advanced stage in which permanent respiratory center damage has occurred The respiratory center responses in this case closely resemble that of long standing pulmonary emphysema with chronic respiratory acidosis in which restoration of the blood bicarbonate level to normal will not correct the abnormally low ventilatory drive In several patients with permanent respiratory center damage associated with polycythemia chronic anoxia and hypercapnia have eventually developed and in 1 case death occurred due to right heart failure (66) Clinically and functionally the end stages of idiopathic polycythemia can thus resemble cor pulmonale with polycythemia secondary to pulmonary disease or to ineffective bellows mechanism In our experience preservation of the maximal breathing capacity and the presence of a normal spirogram will usually differentiate between these various groups although in a preterminal state cardiac failure and pulmonary infection may obviously alter these functions The therapeutic aim in any type of polycythemia therefore should be the reduction of the circulating red cell mass This may be accomplished by phlebotomy or by administration of radioactive phosphorus

It is well recognized that bulbar poliomyelitis brain tumor and a variety of neurologic disturbances may impair the normal ventilatory drive Brain tumors may occasionally cause hyperventilation by abnormal stimulation of the respiratory center But some depression of respiratory center drive is more typical resulting in arterial oxygen unsaturation and arterial hypercapnia due to inadequate ventilation Bulbar poliomyelitis is the best example of this abnormality (53) and the need for artificial respiration is well recognized

Organic damage of the respiratory center in the medulla resulting in a profound lack of respiratory drive may produce many of the features common to ventilatory and alveolorespiratory insufficiency regardless of etiology In a case recently studied that of a patient with severe and diffuse brain damage following trauma hypoventilation was a constant feature The usual ventilatory response to the stimulus of

carbon dioxide added in varying concentrations to inspired air was lacking As a result of his inability to respond to ventilatory stimuli marked arterial oxygen unsaturation with exercise developed and eventually polycythemia and a mild hypercapnia appeared Cardiac catheterization revealed a significant rise of mean pulmonary arterial pressure with exercise In time therefore this patient like any chronically anoxic patient may be expected to manifest cardiac failure due to pulmonary hypertension (63 92) Although eventual cardiac failure of the cor pulmonale type resulting from neurologic defects is uncommon it is nevertheless possible and any patient with a neurologic disease who manifests dyspnea or cyanosis should be observed with that possibility in mind

In summary ventilatory insufficiency due to primary or secondary damage of the respiratory center may progress until the initiating features are masked and elements of both types of respiratory center insufficiency are present

Obviously the clinical features of ventilatory insufficiency in this group of patients may be extremely varied The aims of treatment are therefore directed more to the initiating disease than to the resulting symptomatology However polycythemia when present, must be treated the treatment of respiratory acidosis and cardiac failure should these develop has already been described In deformities of the chest wall respiratory exercises may be of some value in preventing recurrent bronchial infection The milder forms of pulmonary fibrosis probably require no specific therapy ACTH or cortisone therapy ordinarily is not feasible in such cases

PULMONARY FIBROSES WITH DIFFUSION BARRIER

Some patients with roentgenographic evidence of diffuse and scattered lesions of varying size may show some anatomic evidence of pulmonary fibrosis and physiologic proof of interference with oxygen exchange across the alveolocapillary membrane Although many etiologic and pathologic processes may cause this condition the clinical picture and the pulmonary functional aspects are so distinctive that they may be classified as a syndrome—the alveolar capillary block syndrome (4)

Pathologic evidence of alteration in the alveolar walls and capillary membrane has been found in association with clinical states charac

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of a reduction of the total area available for diffusion In several of their cases postmortem examination disclosed thickening of alveolar septums and obliteration of the capillary bed that could well have produced interference with gas diffusion Although in the majority of their cases Baldwin *et al* (7) found significant reduction in residual volume this was not invariably true In 1 case particularly the residual air was significantly elevated this was attributed to the development of cystic disease in areas of organizing fibrosis

Development of the modern technics for study of gas exchange has led to more precise knowledge of the abnormalities in such cases Other workers have described many other diseases with the picture of alveolar capillary block for example beryllium granulomatosis (94) miliary tuberculosis especially in its early phase (56) and pulmonary sarcoid (57 81 86)

Anatomic evidence indicates that thickening of the alveolar walls and of the alveolocapillary membrane is the most common lesion in the majority of cases (4 7 84) Obliteration of pulmonary capillary bed and focal areas of emphysema are also frequently found as are peri vascular collections of granulomas and fibrosis In cases such as metastatic carcinoma involving pulmonary lymphatics vascular tumor thrombi and perivascular areas of fibrosis predominate Occasionally the thickening of the alveolocapillary membrane does not appear to be severe enough to account by itself for the severe alveolorespiratory insufficiency noted clinically It is assumed therefore that a severe loss of surface area secondary to marked shrinkage in lung volumes contributes to the gas diffusion barrier (81) In a sense the most strik ing feature of all these cases is the lack of a uniform pathologic pic ture In one case of pulmonary sarcoid lung biopsy revealed all the features of that disease ranging from areas of purely exudative and granulomatous disease to areas of nonspecific fibrosis and focal emphysema (86) It is such experiences which make precise correla tion of function and anatomy very difficult in any specific case This lack of homogeneity however accounts for the different physiologic disturbances that may be present in this syndrome

Onset in 13 cases of this syndrome observed by our group was insidi ous in the majority but was shortly followed by severely progressive dyspnea with exercise and later with rest (87) Frequent febrile episodes with cough productive of watery to mucopurulent sputums were a feature of advanced disease as was severe weight loss In all of our cases clinical and electrocardiographic evidence of pulmonary hyper

terized by diffuse pulmonary disease with rapidly developing cyanosis and dyspnea and terminating in cardiac failure of the cor pulmonale type (47)

Baldwin Cournand and Richards (7) however were the first to separate these interstitial fibroses of the lung such as the Hamman Rich type from the benign pulmonary fibroses with mild ventilatory insufficiency, and from the emphysema group with alveolorespiratory insufficiency (7) On the basis of the spirogram of lung volume studies of oxygen consumption and of arterial oxygen saturation response to exercise they classified a variety of diseases with a typical clinical and physiologic picture The group included cases of pulmonary fibrosis due to scleroderma or to exposure to asbestos and sulfur dioxide, or associated with a grippe like syndrome and cases of lymphatic carcinoma of the lung Several cases of pulmonary fibrosis with the grippe syndrome closely resembled the Hamman Rich syndrome, clinically and pathologically

In general although the roentgenograms frequently revealed features that were no more impressive than those of the benign fibrosis the patients were severely incapacitated and were profoundly dyspneic even at rest There was marked cyanosis especially with exertion, profound clubbing of the fingers roentgenographic evidence of cardiac enlargement pulmonary hypertension, and often fatal termination Pulmonary function in this group of patients revealed striking reduction of all components of the lung volume (fibrosis pattern) Some degree of ventilatory insufficiency was always present characterized by maximal breathing capacities below normal No evidence of bronchial obstruction was found on the spirograms of most of the patients these cases are therefore characterized by a restrictive type of ventilatory insufficiency Clinically, and by actual measurement extreme hyperventilation was observed even with the mildest exercise Oxygen consumption with exercise was very low and arterial blood studies demonstrated that the oxygen saturation was markedly reduced with mild exercise although at rest it might be within normal limits The carbon dioxide content of the blood in contrast to the severely emphysematous patients was either normal or reduced as a result of the extreme hyperventilation It was concluded that these patients primarily suffer from alveolorespiratory insufficiency rather than from ventilatory insufficiency It was also correctly assumed that the alveolorespiratory insufficiency was a result of impairment of gas diffusion and/or the presence of significant venous admixture or possibly

a definite elevation of residual air and an equally definite reduction of maximal breathing capacity In 1 patient with berylliosis and in 1 with scleroderma obstruction eventually developed as shown by the spirogram this feature is not generally recognized in this syndrome (87) The assumption that the bronchial obstruction was secondary to infection and to the distortion of the bronchial tree by an organizing fibrosis seems reasonable Both focal and bullous emphysema have been noted roentgenographically and pathologically with some regularity in scleroderma berylliosis and sarcoid Such processes if extensive might cause considerable hyperinflation of the lungs and thus elevate the residual air The obliteration of pulmonary blood vessels might also indirectly contribute to the development of emphysema by causing degeneration of alveolar walls with subsequent loss of elastic structure Study of the physical properties of the lung by the described technics might be of great help in assessing pulmonary elastic function in cases of fibrosis

Gas exchange study and analysis of ventilation-perfusion relationships reveal elevated alveolar arterial oxygen gradients at both the room air (venous admixture) and the low oxygen level of inspired air (diffusion gradient) Both types of gradient are invariably present and are frequently of equal magnitude (4) In all cases the oxygen diffusing capacity of the lung is abnormally low The diffusion gradient can be related to the membrane abnormality to the disturbance in ventilation-perfusion relationships if it is severe enough and lastly to actual loss of pulmonary diffusing surface The marked drop in arterial oxygen saturation with exercise is mainly a reflection of diffusion abnormalities The increases in venous admixture and in dead space found in this syndrome contribute to the production of arterial oxygen unsaturation

The pulmonary artery hypertension and low oxygen consumption with exercise have been attributed to an actual reduction in the volume of the pulmonary vascular bed as a result of disease (4) In several of our patients angiocardiography has revealed that the vascular areas are greatly reduced thus supporting this concept (87)

Some of these patients may have normal to slightly elevated pulmonary artery pressures at rest but the pressure rises noticeably with exercise This is probably a reflection both of an organically obstructed pulmonary vascular bed and of the role of an exercise induced anoxia upon the pulmonary artery pressure (4 63)

Although the prognosis in this group is poor careful attention to

tension and cor pulmonale developed and cardiac failure was common

The rather striking physical appearance of the patients is characterized by marked hyperventilation at rest accompanied by liberal use of accessory respiratory muscles due to the limitation of chest cage motion Hyperventilation may persist even in the presence of high oxygen concentrations combined with the other features it is often sufficient to permit a clinical diagnosis of alveolarcapillary block to be made in a cyanotic and acutely dyspneic individual In our experience these patients can usually be distinguished by clinical means from the cases of severe emphysema with alveolorespiratory insufficiency Where facilities for further physiologic study are not available the finding of a normal or lowered carbon dioxide combining power is added evidence that the primary difficulty is due to abnormalities of gas diffusion rather than to emphysema One of the most interesting physical findings in all our cases has been the presence of very fine râles after coughing especially over the lung bases In several of the patients with sarcoid in whom the full blown syndrome later developed these râles were among the earliest signs Their presence together with cough and sputum suggests the presence of secondary bronchiolitis due to poor bronchial drainage The latter could well result from the distortion of small bronchi by the organizing fibrosis Clubbing of the fingers is a fairly constant phenomenon Polycythemia as others (4) have noted tends to be an inconstant feature

The reasons for the variable clinical course are often unclear One of our sarcoid patients in whom a moderate diffusion barrier was noted early has completely recovered Similar observations have been made in healed miliary tuberculosis A miscellaneous group of patients with berylliosis and sarcoid with diffusion barrier are unchanged after 3 years of observation although they are clinically incapacitated right heart failure has not developed In general early onset of cardiac failure determines the rapidity of a fatal outcome This is best illustrated by lymphatic carcinomas of the lung and pulmonary scleroderma In some cases a long course with function unchanged over many years may be due to the relative quiescence of the basic disease as in sarcoid In others such as berylliosis and Hamman Rich disease the early treatment of bronchial infection and the avoidance of stress may account for clinical survival However in most of these cases yearly follow ups have revealed some deterioration of pulmonary function

In time some of the patients in our group may be expected to show

infection and/or cardiac failure is of greater benefit The possible clinical activation or emergence of pulmonary tuberculosis in such patients is an added reason for caution (52) In a few instances such as miliary tuberculosis specific therapy is available which will usually improve the functional picture

Functional Pulmonary Defects Due to Other Conditions

Such varied disease states as cardiac failure mitral stenosis polycythemia and severe anemia may alter pulmonary function (2 18 55 66 73 83) Abnormalities of lung volumes in cardiac failure are well recognized and significant elevation of residual air can occur although low values in the presence of pleural or abdominal effusions have been reported (72) In most of our cases of cardiac failure and severe mitral stenosis there was pronounced elevation of the residual air (87) It may also be elevated in polycythemia vera in this condition phlebotomy may restore the residual air to normal (66) What causes these changes in residual air is obscure but probably is a reflection of changes in the physical properties of the lungs due to congestion Intrathoracic pressure rises in cardiac failure (23) and study of a small group of patients with mitral stenosis suggests that similar abnormalities of lung mechanics exist in that disease (55) The probable defect is rigidity of the lung rather than any primary loss of elasticity and this in turn increases the amount of work needed to ventilate the lungs

Gas exchange may be impaired in these processes and especially in mitral stenosis significant venous admixture gradients may occur with or without significant diffusion gradients and lowered oxygen diffusing capacity (13 87) In a few severe cases of mitral stenosis a clinical and physiologic picture quite similar to that of the patient with alveolocapillary block has been noted (87) Correlation of such findings with organic changes in the pulmonary vascular bed and alveoli as a result of the primary process has been attempted Dyspnea in mitral stenosis may be related to these pulmonary functional abnormalities (18 55) In general even in the patients with gas exchange abnormalities the spirogram and maximal breathing capacity will be fairly normal unless there is complicating pulmonary emphysema Obstruction of major airways therefore does not seem to play a major role Carroll Cohn and Riley (18) however have noted the converse in a few

some of the abnormalities may result in a considerably prolonged life and occasionally in longevity Even mild exercise is definitely harmful because of the induced anoxia and pulmonary hypertension Sedentary activity with periods of rest *is therefore indicated* Patients who follow this regimen obtain some relief of dyspnea and symptomatic improvement The occurrence of bronchial infection and acute bouts of bacterial pneumonia is fairly common antibiotics promptly administered can be lifesaving In 2 of our patients with interstitial pulmonary fibrosis of unknown etiology an acute intercurrent pulmonary infection precipitated the first bout of cardiac failure and of clinically apparent anoxia Prompt treatment with antibiotics and oxygen prevented almost certain death Postinfection study of these patients revealed significant improvement in their cardiopulmonary dynamics

The bronchial disorder observed in this syndrome prompted the routine use of bronchodilating agents in most of the patients in our series Significant improvement has been noted occasionally in the patients with markedly reduced maximal breathing capacities Cardiac failure when it develops is treated in the usual fashion with digitalis sodium restriction and diuretics as needed

Treatment with ACTH or cortisone may be tried but it is difficult to assess the ultimate role and lasting values of steroid therapy In general, the improvement in ventilatory mechanics which may occur lasts only so long as therapy is continued so too does the occasional small rise in oxygen diffusing capacity (81 86) Observations on patients with pulmonary sarcoid manifesting the alveolar capillary block syndrome had suggested that pulmonary function may be unfavorably affected by either ACTH or cortisone therapy Serial observations in a 3 year follow up on 4 such patients have confirmed these early findings (87) It would also seem unlikely that adrenocorticoid therapy could have any effect on a well established pulmonary fibrosis A conservative approach is therefore indicated when such therapy is contemplated We have not used adrenocorticoids routinely in the milder cases especially in those in which the basic disease process tends to be "benign" i e sarcoid In diseases such as scleroderma in which the prognosis is very poor and progress usually rapid cautious trial with ACTH or cortisone is indicated should some symptomatic or functional improvement be noted it is then feasible to maintain such patients indefinitely on adrenocorticoid therapy Acute episodes with sudden drops in arterial oxygen saturation have not responded well to steroids usually treatment of the superimposed bronchopulmonary

pulmonary disease is that it has led to a precise and clear-cut understanding both of the manner of development and the nature of the functional abnormalities in specific diseases As a consequence a more rational therapeutic approach is possible in diseases such as pulmonary emphysema

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cases and postvalvulotomy improvement in the maximal breathing capacity has been observed The mechanism producing venous admixture gradients is due mainly to pulmonary congestion and impaired ventilation-perfusion relations The development of actual anatomic shunts between the precapillary pulmonary vascular bed and pulmonary veins could produce an anatomic venous admixture although direct proof of such shunts is not available Abnormal oxygen gradients in severe anemia and polycythemia vera have also been noted (83 66)

CLINICAL USEFULNESS OF PULMONARY FUNCTION TESTS

Pulmonary function tests cannot be utilized as isolated laboratory tests but must be used in conjunction with careful clinical and fluoroscopic observations Their proper interpretation calls for considerable clinical experience with a wide range of cardiopulmonary disorders The limitations of these tests are that they cannot provide except rarely the basis for an exact anatomic or etiologic diagnosis In addition there may be a striking disproportion between gross roentgenographic evidence of disease and functional disability so that the former cannot be used for estimating the possible functional abnormalities This is not truly a limitation of applied pulmonary physiology and in a sense is an additional indication for more routine use of these tests

Although exact diagnosis in pulmonary disease of unknown etiology cannot be made from these tests pulmonary functional abnormalities may suggest certain groups of diseases and thus narrow the diagnostic considerations In our experience the clinical appearance of disability and the laboratory results are closely correlated and functional tests therefore provide an objective appraisal of a patient s status at any time For this reason they are invaluable in evaluating specific therapy such as the use of steroids in pulmonary sarcoidosis (86) In a large hospital the chief value of these tests is to aid in selecting patients for thoracic surgery and to evaluate the ability of such patients to undergo and survive pulmonary resection thoracoplasty and other surgical procedures Pulmonary cancer bronchiectasis tuberculosis and bullous emphysema cases may require such study Their routine use in these conditions is occasionally academic but the tests unquestionably permit a more objective appraisal of the patient with impaired pulmonary function (25)

In a sense the chief virtue of functional tests in intensive study of

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